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COMMENTARY

Reconsidering Prenatal Hormonal Influences on Human Sexual Orientation: Lessons from Animal Research

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Relying primarily on indirect putative indices of fetal testosterone (T) exposure (2D:4D digit ratios and otoacoustic emissions), Breedlove (2017) summarizes literature supporting the conclusion that lesbian women, on average, are exposed to greater prenatal androgen than are straight women. By contrast, Breedlove argues that homosexual orientation in men (based on these same putative retrospective markers of fetal androgen action) cannot be easily explained by a reduction in prenatal androgen. Instead, Breedlove suggests that there may be, as yet unidentified, brain-specific reductions in response to androgen in male fetuses who grow up to be gay. Breedlove argues persuasively that the non-human animal literature on the critical role of perinatal testosterone exposure in forming male-typical forebrain and/or spinal cord nuclear volume, neuronal number, and neuronal phenotype remains the bedrock reason for suspecting that there must be some link between fetal and/or early postnatal variations in circulating testosterone's neural actions and adult sexual orientation in humans. He points out that in the few documented human examples of sex differences in brain and spinal cord neuronal morphology, the size of the sex differences never approach the magnitude of the homologous morphological sex differences seen in several rodent species as well as ferrets and sheep. Breedlove also alludes to the large animal literature on sex differences in behavior (usually without specifying types of behavior), saying: "Having spent most of my adult life investigating sex differences in behavior in non-human animals, I have wondered whether the results of animal studies have any relevance to sex differences in human behavior."

In so far as the topic of Breedlove's article concerns prenatal influences on human sexual orientation, we were surprised that he barely mentions a sizable animal literature on the hormonal and neural control of male-typical, as well as female-typical, sexual partner preference. The single such animal study cited (Roselli, Larkin, Resko, Stellflug, & Stormshak, 2004) described the interesting correlative observation that a minority (~8% of the population screened) of male sheep (rams), when given a choice between mounting an estrous ewe or another ram, showed a homosexual preference and chose to mount the ram. The volume of a sexually dimorphic nucleus (ovine SDN) located at the border of the medial preoptic area/anterior hypothalamus (mPOA/AH) was significantly greater in heterosexual (gynephilic) rams than in ewes. By contrast, the volume of the SDN in androphilic (homosexual) rams was significantly lower than in gynephilic rams, although its volume was still significantly greater than the SDN of ewes.

As Breedlove points out, it has been difficult to establish either a correlational or a causal linkage between observed sex dimorphisms in forebrain nuclear volume and the capacity of male and female animals to display mating or any other type of social behavior. This is especially true if one restricts the analysis to the motor patterns associated with male copulation. Thus, for example, when given testosterone in adulthood, gonadectomized female, like male, rats display all of the features of male-typical copulation (mounts, intromission-like behaviors, ejaculation-like behaviors) in tests with an estrous female (Emery & Sachs, 1975). Yet, there is a striking twofold–threefold difference (male greater than female) in the dimensions of the SDN nucleus in the rat POA/AH (Gorski, Gordon, Shryne, & Southam, 1978)—a brain region that has long been linked to the display of male copulation in numerous vertebrate species (Hull, Meisel, & Sachs, 2002). There is also disagreement in the literature (Arendash & Gorski, 1983; de Jonge

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et al., 1989) about whether lesions that target only the sexually dimorphic SDN as opposed to the broader expanse of the POA/AH disrupt the capacity of male rats to display copulatory behaviors, per se.

Several studies carried out by one of us (Baum) and collaborators showed that a sex dimorphism also exists in the morphology of the POA/AH of the ferret, a carnivore. In this species, the male possesses a cluster of large, galanin-expressing neurons (male nucleus, MN-POA/AH) which is absent in females (Park, Baum, & Tobet, 1997; Tobet, Zahniser, & Baum, 1986b). In an early study (Cherry & Baum, 1990), small electrolytic lesions that targeted this region caused castrated male ferrets to show a female-typical profile of progressively shorter approach latencies to a stud male (in an L-shaped maze) as the dosage of estradiol benzoate (EB) treatment was increased. The stud male invariably neck gripped and mounted these lesioned male subjects whereupon they showed full-blown female-typical acceptance behavior. When these same lesioned ferrets were given T and tested with an estrous female, they showed only minimal deficits in male-typical mating behavior. In two subsequent studies, adult male ferrets that were castrated in adulthood received bilateral excitotoxic (Paredes & Baum, 1995) or electrolytic lesions (Kindon, Baum, & Paredes, 1996) centered in the Mn-POA/AH. These males were then given chronic treatment with estradiol at the time of testing and displayed a female-typical preference to approach and receive neck grips from a stud male instead of approaching an estrous female in T-maze tests. In contrast, control males in both of these studies showed a robust preference to approach and neck grip the estrous stimulus females.

Paredes, Tzchentke, and Nakach (1998) extended these findings to male rats, in which electrolytic lesions centered in the POA/AH led to an androphilic preference. These results from ferrets and rats strengthen the rationale for further consideration of the possible role of the INAH-3 nucleus (Byne et al., 2000; LeVay, 1991) as part of a larger circuit that controls sexual orientation in humans. In the ferret and rat, the male-typical dimensions of the SDN have been linked to the fetal (ferret) or neonatal (rat) actions of estradiol, formed via the aromatization of circulating T (Cherry, Basham, Weaver, Krohmer, & Baum, 1990; Dohler et al., 1984; Tobet, Zahniser, & Baum, 1986a). It remains to be seen whether perinatal increases in circulating T and/or the formation of estradiol in the human male contribute to male-typical INAH-3 formation and whether this brain structure can be reliably linked with human sexual orientation. On the presumption that 2D:4D digit ratios provide a reliable indication of fetal T exposure, Breedlove argues that the literature points to no significant difference in the male-typical digit ratio values between gay and straight men, suggesting that there is no overall difference in fetal T between these two groups of men. As will be explained below, results of several animal studies suggest that it is perhaps premature to rule out a role for perinatal T exposure/or neural actions in the normal differentiation of brain circuits that control gynephilic and androphilic attractions in human males.

A body of animal literature exists (again, not cited by Breedlove) that links perinatal T exposure to the differentiation of gynephilic partner preference (Adkins-Regan, 1989; Henley, Nunez, & Clemens, 2011). Thus, administering T neonatally to female rats augmented their preference to seek out stimulus females versus males later in life, provided subjects were ovariectomized and given EB or T in adulthood (de Jonge, Muntjewerff, Louwerse, & van de Poll, 1988; Meyerson, Eliasson, & Hetta, 1978). Administering EB over months 3–5.5 caused female pigs to prefer stimulus females over males in adulthood (Adkins-Regan, Orgeur, & Signoret, 1989). Adkins-Regan and Ascenzi (1987) also showed that post-hatch treatment with EB caused female zebra finches to pair bond with other females in adulthood, whereas control females invariably pair-bonded with males. Likewise, in beagle dogs (Beach, Johnson, Anisko, & Dunbar, 1977) and ferrets (Baum, Erskine, Kornberg, & Weaver, 1990), combined prenatal and neonatal administration of T to females led to a later preference to seek out and display male-typical mating behavior with sexually receptive females versus a stimulus male provided that ovarian hormones were given to subjects at the time of adult testing. All of these results support the case for proposing that the gynephilic partner preference seen in lesbian women may be linked to high levels of T exposure/action during perinatal life, as suggested by Breedlove.

In the absence of any consistent demonstration that 2D:4D ratio values are higher in gay men than in straight men, Breedlove argues that one cannot attribute the androphilic orientation of gay men to lower fetal exposure to T. Indeed, reports of longer penis length in gay than straight men (Bogaert & Hershberger, 1999) would be inconsistent with such a conclusion. Breedlove does hold out the possibility that gay men, somehow, are exposed to a reduced action/signaling of T in the fetal nervous system that is not reflected in their genital organ dimensions. He summarizes the data (Blanchard, Cantor, Bogaert, Breedlove, & Ellis, 2006) showing that many (though not all) gay men are born of mothers who had previously gestated more older brothers than had the mothers of straight men. The accumulation of immune system signaling (resulting from the increased number of earlier male pregnancies) in the male fetuses destined to become adult gay men might somehow modify the action of T in the fetal brain. Alternatively, this immune mechanism may act in a manner not associated with T signaling.

It is worth noting that several animal experiments (again, not cited by Breedlove) have shown that neonatal deprivation of T in male mammals attenuated the normal gynephilic partner preference that males normally show in adulthood. Thus, neonatally castrated male hamsters preferred to approach a stimulus male significantly more than males castrated in adulthood, provided estradiol was administered to subjects at the time of testing (Johnson & Tiefer, 1972). Similar results were obtained with neonatal castration of male ferrets (Stockman, Callaghan, & Baum, 1985). Likewise, castration of male pigs on postnatal Day 2 caused them to prefer other males as opposed to estrous females, but again only if estradiol was given at the time of testing (Ford, 1983). Using rats, Bakker, Brand, van Ophemert, and Slob (1993) reported that neonatal treatment with a drug, ATD, that

blocks aromatization of T to estradiol, caused male rats to later prefer to approach a sexually active male over an estrous female in tests given in adulthood after castration and treatment with estradiol. These same males displayed high levels of lordosis behavior in response to male mounts—a behavior rarely displayed by castrated control males in response to male mounting. Likewise, male mice with a null mutation of the gene encoding the aromatase enzyme (ArKO) lost their preference to seek out pheromones from estrous females after adult castration and treatment with estradiol (Bakker, Honda, Harada, & Balthazart, 2004). These same ArKO males did, however, display normal levels of male-typical mating behavior when confined with an estrous female. Taken together, the evidence just summarized points to an essential organizational role of T, perhaps acting after its neural conversion into estradiol, in creating circuits that control gynephilic partner preference in a range of mammalian as well as avian animal models. The perinatal timing of this action of T and/or estradiol differs according to species.

There is also some evidence that the perinatal dosing of steroid hormone action needs to be within some established limits. Thus, in one study (Henley, Nunez, & Clemens, 2010), administration of a high dose of T to male rats over the first 21 postnatal days augmented subjects' later preference to spend time with a stimulus male without diminishing their approach to an estrous female. This enhanced bisexual orientation in T-treated males was accompanied by a striking reduction in the occurrence of all aspects of male-typical mating behavior in tests with an estrous female. Parallel findings were obtained by perinatal administration of T to male ferrets (Baum et al., 1990; Baum & Schretlen, 1975), although in this species early T exposure disrupted only the capacity to attain intromission, perhaps because penile growth was significantly attenuated. These latter findings are especially interesting in light of reports of hypermasculinization of 2D:4D digit ratios (Rahman, 2005), auditory evoked potentials (McFadden & Champlin, 2000), and penis dimensions in gay versus straight men (Bogaert & Hershberger, 1999). We argue, therefore, that contrary to the view expressed by Breedlove, based on an absence of any difference in digit ratios between gay and straight men, it is too soon to rule out variations in the perinatal timing or effectiveness of T's neural actions in organizing circuits that control gynephilic sexual orientation in men.

Finally, we point out that the dogma that female-typical neural and behavioral characteristics develop by default, i.e., in the absence of perinatal actions of sex steroids (Bakker & Baum, 2008), persists even though there is considerable evidence that the female brain (and feminine courtship capacity) is developmentally feminized by estradiol. Thus, feminine receptive behavior (lordosis) was severely reduced in female ArKO mice when tested in adulthood following ovariectomy and treatment with estradiol and progesterone (Bakker, Honda, Harada, & Balthazart, 2002). Interestingly, administration of estradiol benzoate during a specific prepubertal period (between postnatal Days 15 and 25, but not between postnatal Days 5 and 15) almost completely restored lordosis performance in female ArKO mice and augmented their male-directed pheromonal preference (Brock, Baum, & Bakker, 2011). Female mice carrying a targeted mutation in the alpha feto protein gene (AFP-KO) were completely defeminized and partially masculinized (Bakker et al., 2006). Taken together, these results suggest that pre- and early postnatal estradiol action in the developing rodent nervous system leads to male-typical neural and behavioral characteristics, whereas estradiol acts just prior to the age of puberty to promote female-typical brain and behavior development.

Obviously, it remains very challenging to determine whether such different time windows exist for an action of estradiol in sexual differentiation of the human brain. Some suggestion of a feminizing role for prepubertal estradiol in the development of the human brain is derived from women with Turner syndrome (TS; 45, X0). TS is a developmental disorder in which all or part of one X-chromosome is missing, leading to ovarian dysgenesis and low or absent circulating estradiol across the lifespan as one of several phenotypical consequences. In one study (Downey, Ehrhardt, Gruen, Bell, & Morishima, 1989), TS women who received exogenous ovarian hormones beginning shortly after the normal age of puberty were significantly less likely than ovary-intact control women to ever have had a boyfriend or to have engaged in sexual activity with a man. Importantly, the control women in this study were matched with TS women for short stature, which was invariably present in TS women. In another study (Ross, Roeltgen, Feuillan, Kushner, & Cutler, 1998), TS women who began receiving a low dose of estradiol at a prepubertal age showed a significant improvement in their motor function and nonverbal processing speed compared to TS girls given a placebo. More research is needed to determine whether a peripubertal action of estradiol contributes to psychosexual development in women.

Women with complete androgen insensitivity syndrome (CAIS), who invariably have an androphilic orientation (Wisniewski et al., 2000), perhaps provide the best evidence that perinatal T induces a gynephilic orientation in men along with other male-typical structural and functional brain characteristics that depend on the activation of neural androgen receptors across the perinatal lifespan. Thus, CAIS (46 XY) women displayed mental rotation behavior (van Hemmen et al., 2016b) and possessed white matter brain microstructure characteristics (van Hemmen et al., 2016a) that resembled the profiles seen in control women as opposed to control men. As cited by Breedlove, Berenbaum, Bryk, Nowak, Quigley, and Moffat (2009) reported that mean right hand 2D:4D digit ratios in CAIS women resembled those of control women as opposed to control men. This digit ratio finding was recently replicated by van Hemmen, Cohen-Kettenis, Steensma, Veltman, and Bakker (2017), who in addition found that women with CAIS showed a tendency toward female-typical, i.e., larger, click-evoked otoacoustic emission amplitudes in the right ear. These results could be interpreted, as was done by Breedlove, to mean that fetal androgen action controls male-typical click-evoked otoacoustic emission amplitude and digit ratios. It is important to note, however, that in both of these studies the within-group variability of these two

measures was not reduced in women with CAIS compared to control women. In both studies, it was pointed out that the persisting variability in digit ratio and otoacoustic values from CAIS women strongly suggests that additional, non-androgenic factors must make an essential contribution to male-typical sexual differentiation of these variables. It is important to note that CAIS (46 XY) women possess testes that secrete T across the developmental lifespan. Presumably, they also express the aromatase enzyme as well as estradiol receptors in both the developing and adult nervous systems. It is possible that estradiol signaling in the nervous system of CAIS women may, in the absence of any androgen action, contribute to the female-typical characteristics seen in these women, including their androphilic sexual orientation. It is also possible that a yet-to-be-identified reduction in the prepubertal synthesis or action of estradiol in lesbian women may contribute to the development of their gynephilic orientation. Future studies should attempt to address each of these possibilities.

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Compliance with Ethical Standards

Conflict of interest The authors declare no conflict of interest.

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