Prenatal Hormones Are Only a Minor Contributor to Male Brain Structure in Humans

Neil E. Whitehead[1]

[1]Neil E. Whitehead, PhD, is a biochemist who presently works at Whitehead Associates in Lower Hutt, New Zealand. He regularly reviews research on same-sex attraction at www.mygenes.co.nz.

Abstract

The work of Phoenix, Goy, Gerall, & Young (1959) as well as later supporting research has been taken as evidence that the male brain is prenatally masculinized by testosterone but only activated to full heterosexual orientation at puberty. This conclusion was based on experiments in which testosterone was injected into pregnant guinea pigs and the female offspring subsequently examined. It has been widely assumed, though perhaps mistakenly, that a prenatal testosterone surge is also the major cause of male sexual orientation in humans. Subsequent research—including studies of the congenital adrenal syndrome (CAS) in girls—has shown multiple influences from a variety of sources on animal/human adult heterosexual orientation and brain structure, making such a theory too simplistic.

Recent work in the UK (Lombardo et al., 2012), testing the Phoenix et al. theory quantitatively for the first time, is here interpreted to show that the prenatal testosterone effect exists in humans at only 16 to 27% of total influences, so it is weak to modest, not major. Two other types of independent calculation in the Lombardo et al. paper, from twin studies and age of first sexual attraction, support the modest size of the influence. This implies that heterosexuality in humans does not develop solely under the influence of testosterone, but probably requires environmental inputs, which include those from parents and peers.

Homosexuality and transgender orientations have been assumed to be due to prenatal disturbances in testosterone hormone exposure, but the Lombardo et al. result for heterosexuality implies that prenatal influence is at best weak to modest for homosexuality and transgender. The fact that research is increasingly revealing multiple influences makes parenting important and sexual therapy a possibility.

Introduction: Experimental Work by Phoenix et al.

Hormones are important molecules in cells; apart from their various regulatory functions in the adult animal, such as regulation of sexual function, they are involved in the growth and maturation of the fetus. How and to what extent these prenatal hormones—particularly testosterone—influence actual adult sexual behavior has been unclear, and many theories have emerged over the course of time. The purpose of this paper is to discuss the most popular, a theory advanced by Phoenix et al. (1959).

Building on work published by others just before World War II, Phoenix et al. (1959) exposed pregnant guinea pigs to varying amounts of the male sex hormone, testosterone propionate. The male young seemed little different from controls, but the female young with the highest testosterone doses were "hermaphrodites," having masculinized genitalia and showing little or no lordosis, the submissive posture during mating. Further, during mating the adult females tended to mount other females as males would at a 75% rate; that was a very significant difference compared with a rate of 10.5% for female control guinea pigs. These effects resulted in some sense in same-sex attraction (SSA) behavior in the female guinea pigs. In hundreds of subsequent papers by others, this behavior has been equated with sexual orientation. Although this is dubious, because the mental state of the animal is not accessible to observation, this paper allows the equation for the sake of review only.

Changed behavior occurred in six animals out of one experimental group of eight. This immediately shows that the same treatment had variable effects and did not necessarily create the mounting behavior every time. Similarly, the doses sufficient to suppress lordosis in all animals produced hermaphrodites. If testosterone doses were lower and did not produce hermaphrodites, the lordosis was suppressed in only 50% of the animals. The control animals developed opposite-sex attraction (OSA), whereas for SSA, the authors commented, "Within each group the effect on lordosis was not related to the quantity of androgen received prenatally" (p. 373), so the SSA production was quite erratic. That point will be relevant to further discussion of SSA later in this paper.

The impression often given by reports of animal work is that complete and reproducible changes of sexual orientation occur with experimental treatment. In fact, however, such changes in sexual orientation rarely occur with experimental treatment, and there is much overlap in behaviors, regardless of how they are produced. Statistical methods must often be used to detect these differences.

The main conclusion of the authors was about OSA, although their work had produced a kind of SSA. They wrote that there exists "an organizing or 'differentiating' action on the neural tissues mediating mating behavior. During adulthood the hormones are activational" (p. 369).

The guinea pigs did not show sexual attraction characteristics when born; after a period of dormancy, sexual orientation emerged—in other words, was activated—only at puberty. As a result, the theory became known as the *organizational-activational hypothesis*. That hypothesis has been very influential and has been cited at least 950 times. It fits the universal observation that mammalian young of all species show any type of sexual attraction only well after infancy, around the time of puberty. However, the hypothesis raised many questions, particularly whether guinea pig metabolism reflected human metabolism well and whether the experimental results might have merely indicated pathological damage to the central nervous system of the animals.

Subsequent Experimental Work

Relatively little further work was done with the guinea pig, because the rat was a more convenient laboratory animal. But it rapidly became clear that the sensitive period for added hormone exposure was a little different in rats—it was not restricted to prenatal times, but also occurred from just before birth to a few weeks after birth (McCarthy, Wright, & Schwarz, 2009). It also became clear that for rats, the masculinizing hormone needed was not testosterone but estradiol, a hormone more usually associated with the female reproductive system. This showed that the postnatal influence of hormones

could be important for brain development, but this has not been thoroughly investigated for many species. Other work on rats showed there were even strain differences for sensitivity to some sex hormones (McCarthy et al., 2009).

The adult brain differences found in the last several decades were discussed by de Vries (2009). Although anatomical brain sex differences are known for different species, they commented that in most cases we do not understand how or even whether these sex differences contribute to sex differences in behavior. In many species, a brain structure called the sexually dimorphic nucleus (SDN) in the preoptic area (POA)—part of the hypothalamus—is essential for male behavior in many animals, yet surgical procedures that destroy the SDN in male ferrets have no effect (McCarthy et al., 2009). Female ferrets have no SDN nucleus at all, but their behavior can still be manipulated with testosterone, casting doubt on whether the brain structure is even relevant in other species. Mice do not have an SDN difference and still show sexual preferences (de Vries, 2009). Any overview would have to highlight the interspecies diversity that is present. This type of diversity casts further doubt on whether animal models apply to humans.

In a study that showed similar diversity, Schulz, Molenda-Figueira, and Sisk (2009) found evidence in some experimental animals that there was a single extended postnatal sensitive period for steroid-dependent organization of male reproductive behavior; that period began around birth and ended in late adolescence. This was quite different from what occurs in guinea pigs and different from what occurs in rats. They also found that social experience affected both brain and sexual behavior in animals. The primate brain seemed rather similar to the rat brain in its reactions to sex hormones (Wallen, 2005), but, unlike the case for the rat, estradiol was not uniquely important. Some types of masculine behavior seemed completely dependent on maternal socialization; others seemed independent.

Obviously, then, there were differences from one species to another, and some postnatal influence seemed to arise from hormonal effects produced in offspring by

maternal grooming. Even so, it was unclear how strong this effect was compared with the presumed instinct to reproduce. It might be predicted that although humans may have the same basic hormonal framework—such as the importance of steroid sex hormones—the importance of socialization and learning would be much greater and the influence of hormones would be less. *Homo sapiens,* after all, is the learning animal *par excellence*.

Although the varied patterns of animal structure/function should have led to caution, it was popularly assumed that the Phoenix et al. findings applied to humans. It was also assumed that fetal testosterone was an overwhelming influence, because the existence of a prenatal testosterone surge was well known in humans (Hines, 2008) and because young children were not attracted to the opposite sex until around puberty. This implied a complete cessation of hormonal influence during this time, something that seems unlikely. However, as described by Byne and Parsons (1993), even by the mid-eighties—about fifteen years after the work of Phoenix et al.—the academic consensus from all available results was that nature/nurture interaction was the origin of sexual orientation rather than exclusively nature *or* nurture. We must note, then, that a belief in the overwhelming importance of either nature *or* nurture in the scientific literature was not mainstream opinion in the eighties, and still is not.

Human Adrenogenital Syndrome

This section is presented at this point because the work was done a few decades ago and is useful background for current findings. Direct human experimentation, such as testosterone injections into pregnant women, is not ethically possible. However, at least one long-acknowledged medical condition—the congenital adrenogenital syndrome (CAS)—shows the influence of prenatal sex hormones, but its relevance to the Phoenix et al. hypothesis has received little attention.

CAS girls are exposed prenatally to about nine times the normal concentration of androgens as a result of overactive adrenal glands (Wudy, Hartmann, & Homoki, 2000),

and they are born with masculinized genitalia. They are thus very much like the Phoenix et al. guinea pigs that were given the highest testosterone doses. In the guinea pigs, these doses created females that had many male behaviors. In the CAS girls, perhaps the most relevant comparison would be the occurrence of lessened heterosexual orientation, such as lesbian/bisexual sexual orientation. A reasonable estimate of the prevalence of this sexual orientation in CAS girls is about 10 to 20%, and about 10% of CAS girls actually wanted sexual reassignment surgery that would change them to males (Whitehead & Whitehead, 2010). This is a much smaller influence than the 75% of female guinea pigs who mounted other females or the 100% who did not show lordosis; it may be another example of species differences. But these differences suggest that factors other than testosterone may also be important in humans, such as upbringing, peer interaction, and cognitive factors.

Current Evaluation of Phoenix et al.

On the fiftieth anniversary of the publication of Phoenix et al., a 2009 issue of the journal *Hormones and Behavior* was devoted to discussion of the theory. McCarthy et al. (2009) offered the following commentary:

> In this time, the dogma that has emerged is, simply put, that developmental exposure to gonadal steroids acts on the brain to organize the neural substrate that is then selectively activated in the adult to induce expression of sex specific behavior. This elegant synthesis effectively explained a collection of disparate data and provided a framework against which future work could be read. Evidence in support of the essential truths of the hypothesis have [sic] steadily accumulated over the intervening 50 years, but evidence challenging or refuting the hypothesis has piled up in an equally compelling fashion. (p. 1)

They also commented that the field needed clarification, saying, "We do not even know what a female brain is other than it is not male" (p. 6). In their commentary, the authors deplored undue adherence to the "dogma."

In the same volume of *Hormones and Behavior*, Diamond (2009) considered the hypothesis certain for nonhumans and almost certain for humans—a position that seems one of the more extreme unless other influences are also admitted. He mentioned that initially the case of transgender people seemed a refutation of the theory because they were apparently not subject to unusual hormonal conditions *in utero*, as judged by their typical genitalia—but their brains apparently developed a sexual orientation opposed to their chromosomal status. Diamond and others therefore advanced a hypothesis that there was a later period in gestation, after the testosterone surge, during which "brain gender" could be fixed or preprogrammed in the brain in a manner different from the earlier time during which genitalia development needed testosterone. Such a period was found in primates (Wallen & Hassett, 2009), but there remained no direct experimental support in humans. Results reviewed later in the present paper show that, in fact, there is some contrary evidence of such a later period existing in humans. The theory was also incomplete because it did not allow for postnatal hormonal influence, already known for some animal models.

According to a subsequent publication (Semaan & Kauffman, 2010) that described the animal models, the "majority of known sex differences are induced by the sex steroid milieu during early postnatal development" (p. 3). In other words, most sex differences do not originate prenatally. It remained unclear to what extent this applied to humans.

Research on Newborn Children

According to the original theory, although young children have brains prenatally organized as male or female, they do not express sexual behaviors or attractions until puberty (in 1959, when the original theory was postulated, there was little knowledge of

postnatal effects of hormones on the brain). However, researchers still sought for gender-dimorphic behavior in children too young to be affected by parental input. Although there was a slight difference in size between male and female newborn brains, there were very few other differences in actual brain anatomy, and sexual differentiation in brain anatomy seemed to start in a very subtle way only at about age four. It seemed any differences must be at the level of the cell biochemistry rather than the anatomy, though it was also possible that an age of four would have allowed for extensive socialization effects.

However, some behavioral differences are apparently observed. In the first four days after birth, girls imitate parents faster and more often; they also pay more attention to the cries of other babies (Hoffman, 1977). There is a definite difference in sleep/wakefulness maturation that lags in boys (Cornwell, 1993). Newborn girls also have a greater sensitivity to electric shock, react more to a puff of cold air on the skin, and make more fine gestures, according to Nagy, Kompagne, Orvos, and Pal (2007). In all these comparisons, the differences are statistical rather than sharply divided by gender, and there is considerable overlap. The two sexes are more similar than different, but the above features provide some very limited evidence for differences in gender behavior that originate in the brain prenatally. Because of possible environmental influence, comparisons made well after birth may not be valid, and possibly become less valid the later the test.

Human Fetal Testosterone Measurements

The ideal human experiment for comparison with the guinea pigs would be something like measurement of human fetal testosterone and monitoring the children after birth to see if brain structure at puberty reflected the fetal levels. Results of a program of investigation like this have recently been published and are now discussed.

Human fetal testosterone can now be measured during pregnancy in a procedure called *amniocentesis*, in which samples of amniotic fluid are withdrawn from pregnant

women. While the procedure was generally intended for genetic testing, some researchers take advantage of it, after obtaining consent, to analyze the amniotic fluid for testosterone. The levels of testosterone in the fetus show whether there is a prenatal surge and the size of such a surge. Subsequently, some researchers applied a battery of tests to the same children as long as eleven years after they were born to determine whether there was a correlation between testosterone exposure and gendered behavior. Some Dutch research was done, but much of the research comparing fetal testosterone and brain structure at puberty was done in the Autism Research Unit at the University of Cambridge under the direction of well-known chief researcher Simon Baron-Cohen.

Outcome after Birth

In a series of papers over a decade, Baron-Cohen and others have shown correlations (though often small) of fetal testosterone with many male-related traits at various ages. These included correlation inversely with degree of eye contact (Lutchmaya, Baron-Cohen, & Raggatt, 2002a); inversely with greater vocabulary (Lutchmaya et al., 2002b); positively with the 2Digit/4Digit finger-length ratio (Lutchmaya, Baron-Cohen, Raggatt, Knickmeyer, & Manning, 2004); inversely with empathy (Chapman et al., 2006); positively with autism (Auyeung et al., 2009a; Auyeung, Taylor, Hackett, & Baron-Cohen, 2010); positively with male-type child play (Auyeung et al., 2009b; see also Knickmeyer et al., 2005, and van de Beek, van Goozen, Buitelaar, & Cohen-Kettenis, 2009); positively with hand strength (Lust et al., 2011); positively with some visuospatial ability but not mental rotation (Auyeung et al., 2012); and positively with brain lateralization and male-type brain gray-matter features using MRI scans (Mercure et al., 2009; Chura et al., 2010; and Lombardo et al., 2012, the latter paper being particularly important). Some of these tests were done on eight- to eleven-year-old children, obviously long after the fetal testosterone measurements were taken. Any results directly measuring sexual attraction have not thus far been published.

A Correlation Is Found, but Further Research Is Indicated

So we can now test directly whether fetal testosterone correlates with sexually dimorphic anatomical structures, particularly finger-length ratios and brain structure (Lombardo et al., 2012). What is the result? Most importantly, there is a statistically significant correlation between prenatal testosterone exposure and late childhood sexually-dimorphic brain structure, a correlation that supports the organizational/activational hypothesis. However, the results are rather puzzling compared with previous literature. The authors found three sexually dimorphic brain regions in which the gray matter was proportional to fetal testosterone, but the regions are not those traditionally found in sex-difference research, which generally studies the amygdala and the hypothalamus. The authors found the size of the usual sexually dimorphic regions in the amygdala and hypothalamus were not related to fetal testosterone, perhaps because of postnatal hormonal influence. On the other hand, one region in the amygdala whose size was related to fetal testosterone was not sexually dimorphic. This is not what those in the field would expect, and replication would be reassuring.

Those who have followed similar studies over the last few decades will be hesitant to accept these brain structure results until replicated, because much brain structure work has failed that test. For the purposes of this paper, however, the results are tentatively accepted.

Although the authors emphasize that their work shows a link between fetal testosterone and brain regions, they do not think testosterone is the only influence. They invoke later—in other words, postnatal—androgen surges, epigenetic effects (influences from the environment), and a possible influence from placental sex hormones. This again demonstrates the current thinking that multiple influences are involved.

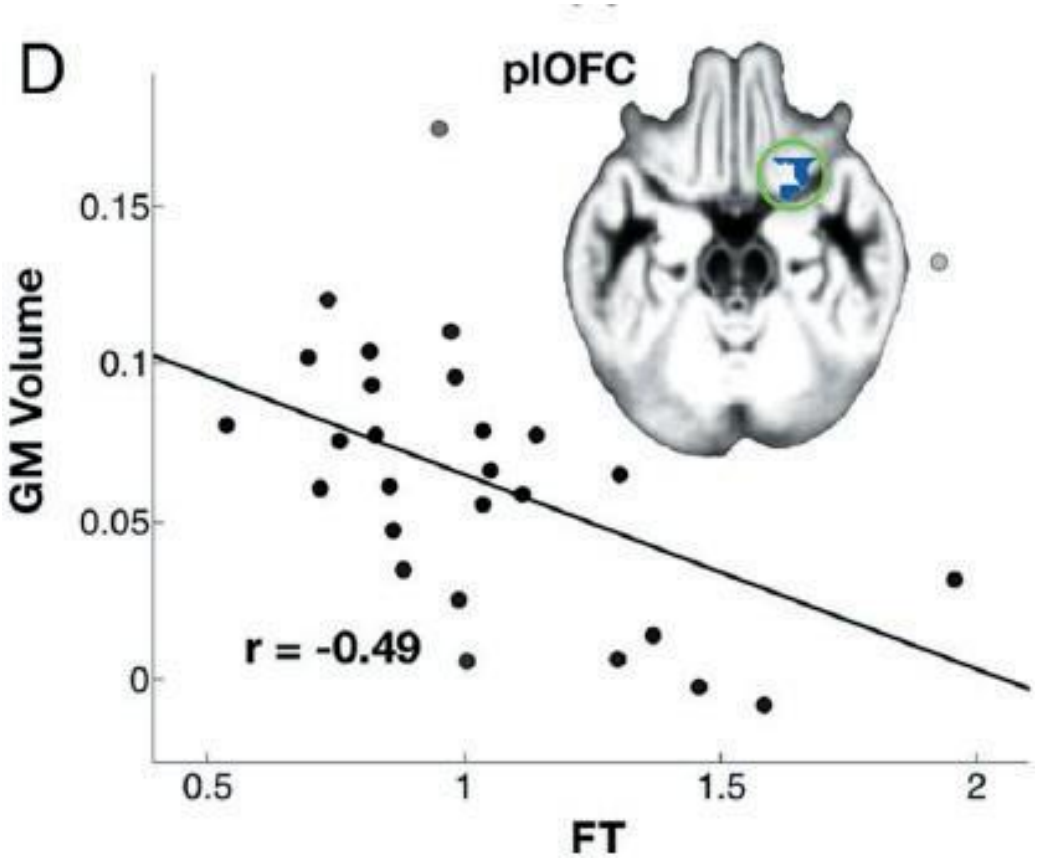

Figure 1.The (negative) association between one brain region (gray matter volume of posterior lateral orbito-frontal cortex) and fetal testosterone. Taken from Lombardo et al. (2012). The pale green circle encloses the blue-colored area that is the relevant brain region.

Strength of the Correlation

The data scatter, hence the strength of the correlation, is identical for the three brain regions within error. Correlation coefficients range from 0.45 to 0.49 (compared with a maximum 1.0 for perfect correlation), a statistically real effect. However, looking at Figure 1, it is clear that there is quite a degree of scatter in the relationship and probably a lognormal distribution; the strength of the correlation may be overstated. The brain structure gray matter volume is not rigidly dependent on the fetal testosterone. (A similar strength of correlation is found for the finger-length ratios.)

To find the degree of influence, fraction of variance explained, or scatter explained by the regression, the correlation coefficient is squared. That shows only 16 to 27% of the total variance (roughly total influences) on finger-length ratio and brain structure is explained by fetal testosterone; 73 to 84% is left unexplained. This makes the fetal testosterone influence weak to modest at best. The authors do not go as far as mentioning that or other possible implications.

The above calculation used the maximum correlations from the published papers of the Dutch and UK researchers. The other correlations between fetal testosterone and later male traits, such as autism, were much weaker or nonexistent; therefore, many proposed links are not supported by experiment. Another major caveat is that the brain scans were done well after the known human six-month *post*birth testosterone surge, which was not assessed by Simon Baron-Cohen and his team. The fetal testosterone association could ultimately prove to be weaker in its effects than the postbirth testosterone association.

An Adequate Test of the Organizational-Activational Hypothesis?

The paper by Lombardo et al. is particularly important because the researchers explicitly put their research forward as a test of the Phoenix et al. hypothesis for the brain—the idea that the "male brain" is fully organized prenatally but activated at puberty. At this point, some readers may be puzzled that the testing on the children was done between the ages of eight and eleven—that is, before puberty. The authors did agree in the text that puberty would be an important area of focus for future work and would probably involve a more precise test.

Two comments should be made. First, it was possible that even in late childhood there would be some correlation, and that is exactly what the authors found. This result almost demanded to be published. The second is more complicated: eight to eleven may have been an appropriate age range because quite significant literature now maintains that

the average age of first attraction—hence sexual orientation—to either the opposite sex or same sex is not at puberty. Instead, it is *before* puberty—at ten years, with a very wide age range of several years (Herdt, McClintock, Henderson, Lehavot, & Simoni, 2000). This "first attraction" might be merely hero-worship or a child's crush on a teacher but, on the other hand, it could be a real pre-echo of genuine attraction. Lombardo et al. do not explicitly give this as a rationale for testing at ages eight to eleven; however, the age of ten is conveniently covered by the age range they used.

Is it likely that better correlations may be achieved at puberty? We will have to wait and see, but in view of the existence of other influences that usually tend to reduce correlations rather than increase them, this is not likely. It is also possible that a testosterone/brain structure correlation like the one found by Lombardo et al. does not lead inevitably to a particular attraction (as in the case of the ferrets mentioned previously), so this is another reason the final association between fetal testosterone and attraction may be weaker than expected or may not exist at all.

Implications of the Modest Correlation with Fetal Testosterone

Some of the more extreme proponents in the research community may have expected to find an overwhelmingly strong testosterone/brain structure correlation, but it was actually surprisingly weak. It may be that other hormones are important and the focus of attention has been misplaced. This has important implications; although most research finds there is a correlation between fetal testosterone and later maleness, it does not *rigidly prescribe male brain structure but only modestly influences it.*

The important conclusion is this: *Heterosexual brain dimorphism seems only modestly prenatally prescribed by prenatal testosterone.* We now discuss two other independent lines of research that are consistent with that result.

Other Research Evidence for Modest Influence

The fetal/brain research gave a testosterone influence of 16 to 27%. There is very little other research that tries to estimate the quantitative strength of prenatal factors on heterosexual attraction, but one paper that did used twin studies (Hershberger, 1997). Although there is some slight doubt that testosterone in the womb is exactly the same even for identical twins, these studies are generally accepted. A weak to modest result (18 to 26%) for the influence of all prenatal factors on OSA was found. The sample was unmarried adults and was unusually favorable for testing heterosexual development. Calculations of the genetic influence on OSA from usual whole-population twin samples encounter intractable mathematical problems because relatively few respondents of minority sexual orientations are present; in an unmarried sample the percentage is much higher. Hershberger therefore was able to use this twin study to calculate the total prenatal influence on OSA.

This type of study is particularly important because twin studies test all prenatal factors combined, not just genetics or prenatal hormones. They include any effects of a theoretical later time in gestation when the brain might be preprogrammed independently of the earlier testosterone surge, as proposed by Diamond and others.

A result of this modest strength at the lower end of the range is similarly found when one investigates the wide spread of ages in first OSA attraction (Whitehead, submitted; see also Whitehead & Whitehead, 2010, p. 34). The wider the age spread in the appearance of any trait, the less likely it is to be genetic or biologically programmed, and the large spread for OSA makes the calculated degree of prenatal programming similar to the first two approaches—and a minor factor. These three similar results are shown in Figure 2.

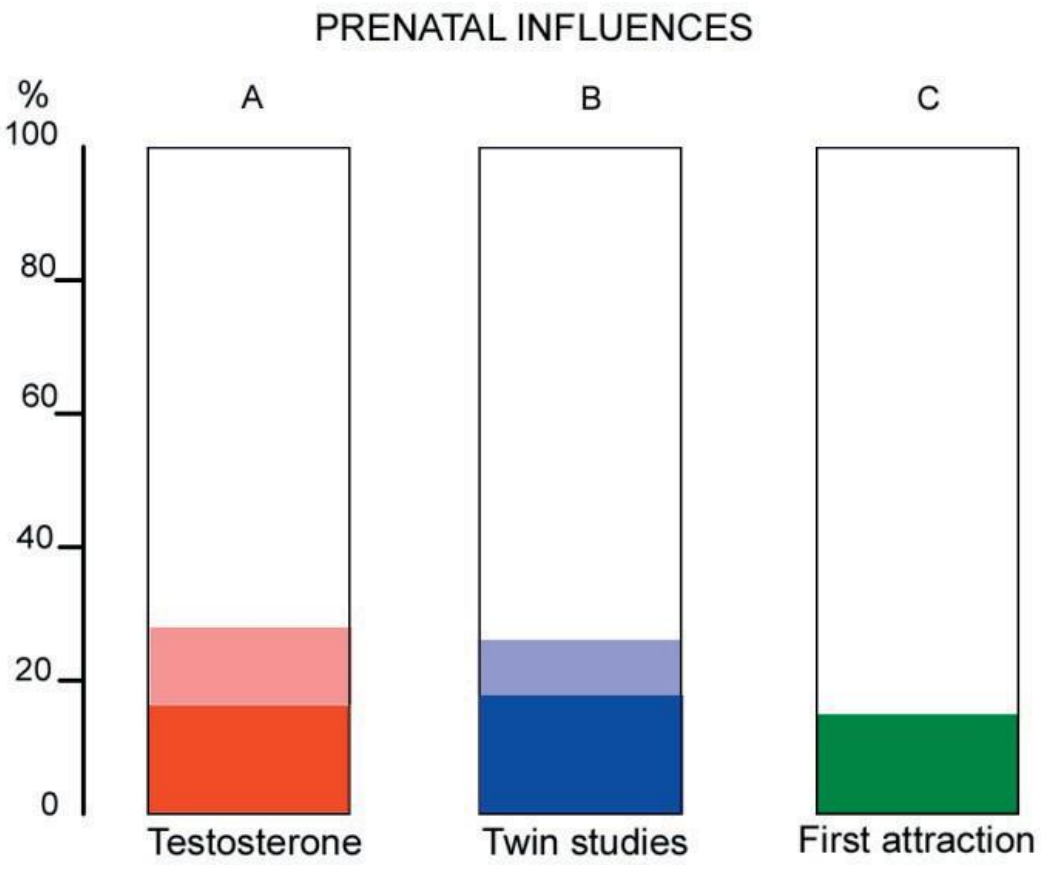

Figure 2.Percentage of prenatal influences on OSA as shown by (A) testosterone from amniocentesis, (B) twin studies, (C) age spread of first attraction. Shaded areas are 95% confidence limits where known.

The twin studies are the summation of all prenatal influences on adult sexual orientation. The testosterone results are only the influence of testosterone on sexually dimorphic brain structure, and are therefore more restricted. (For the purposes of this paper, it is assumed that adult sexual orientation is related to dimorphic brain structure, as the Phoenix et al. scheme proposes.) The similarity is important because of the hypothesis of Diamond (2009), mentioned earlier, that a prenatal influence independent of testosterone is important for sexually dimorphic brain structure. The similarity of A and B above means that the testosterone entirely accounts for the quite limited effects on the brain and that there is no room for another influence, as posited by Diamond.

We also note that the strength of the masculinizing influence for the CAS girls is 10 to 20%, consistent with the values discussed above. Studies on non-CAS girls from those born following amniocentesis would also be very useful in understanding female OSA, but the Hershberger twin studies indicate any prenatal influence on females is also weak to modest, as with the male results, and it is likely that the influence on female brain structure is similarly very modest.

What Does This Modest Effect Mean for Homosexual and Transgender Attraction?

The comparison of A and B in Figure 2 means that there is no room for a late-gestation influence on OSA. An unexpected corollary is that the transgender hypothesis of late gestational unusual brain programming—as proposed by Diamond (2009) and mentioned earlier—is not very likely. As shown in Figure 2, the late gestation period is not significantly involved in establishing OSA in humans and is therefore not likely to be involved in transgender origins either.

There is an independent implication in all this for the development of SSA, although only heterosexual orientation was examined in the Lombardo et al. paper. It has been popular to argue that SSA is prenatally programmed in humans and that the mechanism for males would probably be a lesser amount of testosterone at critical prenatal times. Such a mechanism, with its variable possible amounts of testosterone from slightly deficient to very deficient, would be expected to less tightly correlate with the final brain structure and therefore have an effect certainly not stronger than the effect on OSA, and more likely weaker. One therefore expects that the association between fetal testosterone and supposed SSA-related brain structure *should be less influenced by prenatal hormones than is OSA, so that the effect of prenatal hormones should be weak to modest, at best—not dominant.*

Other Factors in Sexual Orientation Development

For the first time, we have quantitative evidence about the strength of prenatal hormone influence on sexually dimorphic brain structure. This was expected by many to be overwhelmingly strong for humans, but instead it seems that testosterone is just one factor among several. Following is a list of some of the other influencing factors found in other research, but in all cases they are not individually predominant. The picture is therefore of many influences of modest strength working together on the brain—not just during fetal development but after birth through adolescence. Because the multiple factors may interact in many ways and could add or multiply their effects, accurate prediction of final sexual orientation based on these factors is at present too complex.

Research has increasingly revealed many other processes at work in the development of sexual orientation/attraction in humans. Since the time of the Phoenix et al. paper, researchers have discovered that there are some prenatal sexually dimorphic effects in the brain that depend directly on the sex chromosomes (Lenz, Nugent, & McCarthy, 2012), even where there is no influence of sex hormones and even in disorders of sexual development in which there are no gonads. Estrogen proves essential for feminization of the brain—females are not simply default males (Lenz et al., 2012). Testosterone masculinizes males, but there is also an independent process of defeminization (Lenz et al., 2012). There may be contribution from sex hormones produced in the placenta, and at birth there are high levels of sex hormones in the brain independent of circulating hormones and produced from cholesterol (Konkle & McCarthy, 2011). There is a male testosterone surge in humans just after birth that lasts much longer than the prenatal one; there is a corresponding estradiol surge for females (Winter, Hughes, Reyes, & Faiman, 1976). Some brain masculinization occurs *after* birth (Lenz et al., 2012). Sexually dimorphic human brain changes at puberty seem proportional to the sex hormone levels at that time (Neufang et al., 2009); this implies the importance of current hormone levels and not just prenatal influences. Further, since

maternal care significantly influences future sexual orientation, at least in rats (Moore, 1992), there is a general consensus that there are multiple influences at work rather than solely the prenatal testosterone surge.

This leads to a contemporary comment on the "organizational-activational hypothesis" Phoenix paper: "Our current knowledge of sex-based neurobiology has outgrown this simplistic model. Multiple lines of research have contributed to this conclusion" (Reinius, 2011, p. 15).

For therapists, this conclusion should reinforce the idea that therapy in the field of sexual orientation is a possible option. Such therapy will not encounter impassable barriers through brain structures already formed *in utero* that are, of course, unalterable.

The conclusion also has possible implications for parents. They cannot merely assume that heterosexuality will automatically develop in their children. As always, guidance and direction are a continuing part of parenting.

In a succeeding paper, the author hopes to discuss a further influence on brain structure—death of neurons in a sexually dimorphic way up to adulthood and unrelated results now available using gene expression measurements for the whole genome—to show the degree of sexual dimorphism in the brain at various ages. These support the interpretation in this paper.

Conclusion

The contribution of prenatal sex hormones to OSA or SSA is not anywhere near 100%, as many have believed, but is at most about 25%—in other words, a minor contribution. In that sense, one is not born straight or gay or transgender.

Simply stated, the prenatal hormonal contribution to heterosexual brain structure is weak to modest. Similarly, prenatal contribution to homosexual or transgender brain structure is weak to modest.

References

Auyeung, B., Baron-Cohen, S., Ashwin, E., Knickmeyer, R., Taylor, K., & Hackett, G. (2009a). Fetal testosterone and autistic traits. *British Journal of Psychology, 100*(1), 1–22.

Auyeung, B., Baron-Cohen, S., Ashwin, E., Knickmeyer, R., Taylor, K., Hackett, G., & Hines, M. (2009b). Fetal testosterone predicts sexually differentiated childhood behavior in girls and in boys. *Psychological Science, 20*(2), 144–148.

Auyeung, B., Knickmeyer, R., Ashwin, E., Taylor, K., Hackett, G., & Baron-Cohen, S. (2012). Effects of fetal testosterone on visuospatial ability. *Archives of Sexual Behavior, 41*(3), 571–581.

Auyeung, B., Taylor, K., Hackett, G., & Baron-Cohen, S. (2010). Foetal testosterone and autistic traits in 18- to 24-month-old children. *Molecular Autism, 1*(1), 11.

Byne, W., & Parsons, B. (1993). Human sexual orientation: The biologic theories reappraised. *Archives of General Psychiatry, 50*, 228–239.

Chapman, E., Baron-Cohen, S., Auyeung, B., Knickmeyer, R., Taylor, K., & Hackett, G. (2006). Fetal testosterone and empathy: Evidence from the empathy quotient (EQ) and the "reading the mind in the eyes" test. *Social Neuroscience*, *1*(2), 135–148.

Chura, L. R., Lombardo, M. V., Ashwin, E., Auyeung, B., Chakrabarti, B., Bullmore, E. T., & Baron-Cohen, S. (2010). Organizational effects of fetal testosterone on human corpus callosum size and asymmetry. *Psychoneuroendocrinology, 35*(1), 122–132.

Cornwell, A. C. (1993). Sex differences in the maturation of sleep/wake patterns in high risk for SIDS infants. *Neuropediatrics, 24*, 8–14.

deVries, G. J. S. P. (2009). Sex differences in the brain: The relation between structure and function. *Hormones and Behavior, 55*(5), 589–596.

Diamond, M. (2009). Clinical implications of the organizational and activational effects of hormones. *Hormones and Behavior, 55*(5), 621–632.

Herdt, G., McClintock, M., Henderson, A. W., Lehavot, K., & Simoni, J. M. (2000).The magical age of 10. *Archives of Sexual Behavior, 29*(6), 587–606.

Hershberger, S. L. (1997). A twin registry study of male and female sexual orientation. *Journal of Sex Research, 34*, 212–222.

Hines, M. (2008). Early androgen influences on human neural and behavioural development. *Early Human Development, 84*, 805–807.

Hoffman, M. L. (1977). Sex differences in empathy and related behaviors. *Psychological Bulletin, 84*(4), 712–722.

Knickmeyer, R. C., Wheelwright, S., Taylor, K., Raggatt, P., Hackett, G., & Baron-Cohen, S. (2005). Gender-typed play and amniotic testosterone. *Developmental Psychology, 41*, 517–528.

Konkle, A. T., & McCarthy, M. M. (2011). Developmental time course of estradiol, testosterone, and dihydrotestosterone levels in discrete regions of male and female rat brains. *Endocrinology, 152*(1), 223–235.

Lenz, K. M., Nugent, B. M., & McCarthy, M. M. (2012). Sexual differentiation of the rodent brain: Dogma and beyond. *Frontiers of Neuroscience, 6*, 1–12.

Lombardo, M. V., Ashwin, E., Auyeung, B., Chakrabarti, B., Taylor, K., Hackett, G., Baron-Cohen, S. (2012). Fetal testosterone influences sexually dimorphic gray matter in the human brain. *Journal of Neuroscience, 32*(2), 674–680.

Lust, J. M., Geuze, R. H., Van de Beek, C., Cohen-Kettenis, P. T., Bouma, A., & Groothuis, T. G. (2011). Differential effects of prenatal testosterone on lateralization of handedness and language. *Neuropsychology, 25*(2), 581–589.

Lutchmaya, S., Baron-Cohen, S., & Raggatt, P. (2002a). Foetal testosterone and eye contact in 12-month-old human infants. *Infant Behavior and Development, 25*, 327–335.

Lutchmaya, S., Baron-Cohen, S., & Raggatt, P. (2002b). Foetal testosterone and vocabulary size in 18 and 24 month infants. *Infant Behaviour and Development, 24*, 418–424.

Lutchmaya, S., Baron-Cohen, S., Raggatt, P., Knickmeyer, R., & Manning, J. T. (2004). 2nd to 4th digit ratios, fetal testosterone and estradiol. *Early Human Development, 77*, 23–28.

McCarthy, M. M., Wright, C. L., & Schwarz, J. M. (2009). New tricks by an old dogma: Mechanisms of the organizational/activational hypothesis of steroid-mediated sexual differentiation of brain and behavior. *Hormones and Behavior, 55*(5), 655–665.

Mercure, E., Ashwin, E., Dick, F., Halit, H., Auyeung, B., Baron-Cohen, S., & Johnson, M. H. (2009). IQ, fetal testosterone and individual variability in children's functional lateralization. *Neuropsychologia, 47*(12), 2537–2543.

Moore, C. L. (1992). The role of maternal stimulation in the development of sexual behavior and its neural basis. *Annals of the NY Academy of Sciences, 662*, 160–177.

Nagy, E., Kompagne, H., Orvos, H., & Pal, A. (2007). Gender-related differences in neonatal imitation. *Infant and Child Development, 16*(3), 267–276.

Neufang, S., Specht, K., Hausmann, M., Gunturkun, O., Herpertz-Dahlmann, B., Fink, G. R., & Konrad, K. (2009). Sex differences and the impact of steroid hormones on the developing human brain. *Cerebral Cortex, 19*(2), 464–473.

Phoenix, C. H., Goy, R. W., Gerall, A. A., & Young, W. C. (1959). Organizing action of prenatally administered testosterone propionate on the tissues mediating mating behavior in the female guinea pig. *Endocrinology, 65*, 369–382.

Reinius, B. (2011). *Sexually Dimorphic Gene Expression in the Mammalian Brain*. (Unpublished doctoral dissertation).University of Uppsala, Uppsala, Sweden.

Schulz, K. M., Molenda-Figueira, H. A., & Sisk, C. L. (2009). Back to the future: The organizational–activational hypothesis adapted to puberty and adolescence. *Hormones and Behavior, 55*(5), 597–604.

Semaan, S. J., & Kauffman, A. S. (2010). Sexual differentiation and development of forebrain reproductive circuits. *Current Opinions in Neurobiology, 20*(4), 424–431.

van de Beek, C., van Goozen, S. H. M., Buitelaar, J. K., & Cohen-Kettenis, P. T. (2009). Prenatal sex hormones (maternal and amniotic fluid) and gender-related play behavior in 13-month-old infants. *Archives of Sexual Behavior, 38*(1), 6–15.

Wallen, K. (2005). Hormonal influences on sexually differentiated behavior in nonhuman primates. *Frontiers in Neuroendocrinology, 26*(1), 7–26.

Wallen, K., & Hassett, J. M. (2009). Sexual differentiation of behaviour in monkeys: Role of prenatal hormones. *Journal of Neuroendocrinology, 21*(4), 421–426.

Whitehead, N. E., & Whitehead, B. K. (2010). *My Genes Made Me Do It!* (2nd ed.). Lower Hutt, New Zealand: Whitehead Associates. Also downloadable from www.mygenes.co.nz.

Winter, J. S., Hughes, I. A., Reyes, F. I., & Faiman, C. (1976). Pituitary-gonadal relations in infancy: 2. Patterns of serum gonadal steroid concentrations in man from birth to two years of age. *The Journal of Clinical Endocrinology and Metabolism, 42*(4), 679–686.

Wudy, S. A., Hartmann, M., & Homoki, J. (2000). Hormonal diagnosis of 21-hydroxylase deficiency in plasma and urine of neonates using benchtop gas chromatography-mass spectrometry. *Journal of Endocrinology, 165*(3), 679–683.