Introduction: The brain-sex theory of transsexualism

The theory that transsexualism reflects a neurological intersex condition, in which one or more sexually dimorphic areas of the brain are inconsistent with somatic sex, is sometimes called the "brain-sex" theory of transsexualism. This theory rests largely on two reports from the Netherlands Institute for Brain Research, published in 1995 and 2000, that suggested a possible neuroanatomical marker for transsexualism in the brain.

In 1995, Zhou, Hofman, Gooren, and Swaab reported that a collection of cells in the hypothalamus, called the central subdivision of the bed nucleus of the stria terminalis (BSTc), was sexually dimorphic in humans. Based on postmortem studies, Zhou et al. found that the average volume of the BSTc in males was about 44% larger than in females. In six male-to-female (MtF) transsexuals who had undergone feminizing hormone therapy, however, the average volume of the BSTc was within the typical female range. Zhou et al. noted that the six transsexuals they studied varied in their sexual orientations and concluded that there was "no relationship between BSTc size and the sexual orientation of transsexuals" (p. 70). Based on additional postmortem examinations conducted in a small number of nontranssexual patients with abnormal hormone levels, Zhou et al. further concluded that "the small size of the BSTc in male-to-female transsexuals cannot be explained by adult sex hormone levels" (p. 70).

In 2000, Kruijver et al. published a follow-up study in which they looked at the number of neurons in the BSTc rather than its volume. Kruijver et al. examined tissue from the same six MtF transsexuals studied by Zhou et al.; they also looked at tissue from one female-to-male (FtM) transsexual and from an 84-yr-old man who "had very strong cross-gender identity feelings but was never . . . sex-reassigned or treated . . . with estrogens" (p. 2039). Kruijver et al. found that BSTc neuron number was even more sexually dimorphic than BSTc volume: The average BSTc neuron number in males was 71% higher than in females. Once again, the six MtF transsexuals showed a sex-reversed pattern, with an average BSTc neuron number in the female range. BSTc neuron number was also in the female range in the untreated gender dysphoric male and was in the male range in the FtM transsexual. Again, the putative sexual orientation of the MtF transsexuals seemed to make no difference. Data from the few nontranssexual patients with abnormal hormone levels led Kruijver et al. to conclude that "hormonal changes in adulthood did not show any clear
relationship with the BSTc . . . neuron number” (p. 2039).

A challenge to the brain-sex theory

In 2002, the brain-sex theory of transsexualism was seriously challenged by some unexpected findings published by Chung, De Vries, and Swaab. They observed that significant sexual dimorphism in BSTc volume and neuron number does not develop in humans until adulthood. Most MtF transsexuals, however, report that their feelings of gender dysphoria began in early childhood (e.g., Lawrence, 2003). It is difficult to see how the volume and neuron number of the BSTc could be neuroanatomical markers for gender identity if they have not yet become sexually dimorphic by the time cross-gender feelings have become apparent. Recognizing this difficulty, Chung et al. wrote:

Late sexual differentiation of the human BSTc volume also affects our perception about the relationship between BSTs [sic] volume and transsexuality. . . . Epidemiological studies show that the awareness of gender problems is generally present much earlier. Indeed, [about] 67-78% of transsexuals in adulthood report having strong feelings of being born in the wrong body from childhood onward. (p. 1032)

It is still possible to imagine explanations of these findings that would be consistent with the hypothesis that BSTc volume and neuron number in adulthood are markers for gender identity in transsexuals. Chung et al. (2002) conjectured that fetal or neonatal hormone levels could affect gender identity and could also produce changes in BSTc "synaptic density, neuronal activity, or neurochemical content" (p. 1032) that might not affect BSTc volume or neuron number immediately, but might do so during adulthood. Alternatively, they suggested, failure to develop a gender identity consistent with one's somatic sex might affect adult BSTc volume and neuron number by some unspecified mechanism.

Current status and implications of the brain-sex theory

Despite the significant questions raised by Chung et al. (2002), the brain-sex theory of transsexualism continues to have some supporters. For example, Gooren (2006), after summarizing the Zhou/Kruijver data, concluded that, "These findings support a concept that transsexualism is a sexual differentiation disorder of the sex dimorphic brain" (p. 598).

Because the brain-sex theory is a "unitary" theory of transsexualism, it appears to contradict another widely accepted theory, proposed by Blanchard (1989a, 1989b, 2005), that there are two distinctly different subtypes of MtF transsexuals, homosexual and nonhomosexual, with different clinical presentations and different etiologies. According to Blanchard's typology, homosexual MtF transsexuals, who are exclusively sexually attracted to men, seek sex reassignment primarily because their appearance and behavior are markedly gender-atypical. Nonhomosexual MtF transsexuals, who may be sexually attracted to women, to women and men, or to persons of neither sex, are not marked gender-atypical in their appearance or behavior; they are believed to seek sex reassignment primarily because they are sexually attracted to the idea of becoming women, a paraphilic sexual interest that Blanchard (1989a) called autogynephilia. Individuals who oppose Blanchard's formulation tend to favor the brain-sex theory, which postulates that there is a neuroanatomical basis for female gender identity in MtF transsexuals that is independent of sexual orientation.

A critique of the brain-sex theory of transsexualism

How can data from seven (or perhaps eight) transsexual brains be reconciled with
Blanchard's transsexual typology, which is now accepted by most knowledgeable clinicians and researchers? There are at least three plausible alternative explanations of the Zhou/Kruijver findings:

- First, but probably least likely: The Zhou/Kruijver findings might reflect the chance selection of a sample of MtF transsexual brains with unrepresentative BSTc volumes and neuron numbers.
- Second, and somewhat more likely: Because all six MtF transsexuals in the Zhou/Kruijver studies were probably nonhomosexual, their atypical BSTc volumes and neuron numbers might be markers for nonhomosexual MtF transsexualism specifically, but not for MtF transsexualism generally.
- Third, and most likely: The Zhou/Kruijver findings might reflect the effects of feminizing or masculinizing hormone therapy, which all six MtF transsexuals and the one FtM transsexual received.

I will consider these alternative explanations in turn.

**A possible explanation, but least likely: The Zhou/Kruijver results might reflect the chance selection of a sample of MtF transsexual brains with unrepresentative BSTc volumes and neuron numbers**

Examination of the Zhou/Kruijver data reveals considerable variability in BSTc volume and neuron number within each of the groups they studied (i.e., MtF transsexuals, heterosexual men, homosexual men, and women). Could it be that there is really no difference in average BSTc volume and neuron number between nontranssexual men and MtF transsexuals and that the differences found in the Zhou/Kruijver studies merely reflected the chance selection of a highly unrepresentative group of MtF transsexuals?

Statistical testing provides an estimate of the likelihood of such an occurrence. In the case of BSTc volume, the observed difference in mean values between the MtF transsexual group and the heterosexual male group would be expected to occur by chance less than one time in 200 ($p < .005$; Zhou et al., 1995, p. 69). In the case of BSTc neuron number, the probability is greater, but still less than one time in 25 ($p < .04$; Kruijver et al., 2000, p. 2036).

But these statistical tests assume that the relevant comparisons were planned prior to examination of the data, i.e., that Zhou et al. (1995) had hypothesized in advance that BSTc volume would be sex-atypical in MtF transsexuals. It appears, however, that this was not the case. Instead, Zhou et al. apparently set about examining sexually dimorphic structures in the brain, looking for one for which MtF transsexuals might be sex-atypical. They wrote,

> We searched for a brain structure that was sexually dimorphic but that was not influenced by sexual orientation, as male-to-female transsexuals may be "oriented" to either sex with respect to sexual behavior. . . . Although there is no accepted animal model for gender-identity alteration, the bed nucleus of the stria terminalis (BST) turned out to be an appropriate candidate to study . . . (p. 68)

When statistical comparisons are suggested by examination of the data, as they appear to have been in the Zhou/Kruijver studies, they are not true tests of hypotheses in a scientifically rigorous sense. The findings of such studies must be replicated before they can be accepted with confidence. So far, no one has attempted to replicate the Zhou/Kruijver findings.

The importance of replicating findings of this kind is underscored by the history of attempts
to replicate initial reports of sexual dimorphism in the volume of other hypothalamic nuclei. Swaab and Fliers (1985) and Hofman and Swaab (1989) reported that the volume of a human hypothalamic nucleus now called INAH 1 was sexually dimorphic; these findings seemed unlikely to be due to chance alone (p < .001; Hofman & Swaab, p. 60). But neither Allen, Hines, Shryne, and Gorski (1989), nor LeVay (1991), nor Byne et al. (2000) could confirm sexual dimorphism in the volume of INAH 1. Allen et al. reported that the volume of yet another human hypothalamic nucleus, INAH 2, was sexually dimorphic; these findings, too, seemed unlikely to be due to chance alone (p < .03; p. 499). But neither LeVay nor Byne et al. could confirm sexual dimorphism in the volume of INAH 2. These results illustrate why it is essential that neuroanatomical findings of this kind be replicated before being accepted.

A more likely explanation: The female-typical BSTc volume and neuron number observed in the MtF transsexuals are markers for nonhomosexual or autogynephilic MtF transsexualism, not for MtF transsexualism generally

Even if the Zhou/Kruijver findings do not simply represent the chance selection of an unrepresentative group of MtF transsexual brains, they are probably still consistent with Blanchard's transsexual typology, because all six MtF transsexuals studied were likely to have been nonhomosexual or autogynephilic transsexuals. Consequently, a female-typical BSTc volume and neuron number might simply be a marker for nonhomosexual transsexualism or for autogynephilia.

Before considering the sexual orientation of the six MtF transsexuals, we should recall that, according to Blanchard's typology, MtF transsexuals who are sexually attracted to women, to women and men, or to persons of neither sex, are considered nonhomosexual. Only MtF transsexuals who are exclusively sexually attracted to men are considered to be homosexual MtF transsexuals. But not all MtF transsexuals who describe themselves as sexually attracted to men are genuinely homosexual: It is widely recognized that some nonhomosexual MtF transsexuals inaccurately describe themselves as sexually attracted to men, because they misinterpret sexual arousal to the idea of being a woman having sex with a man as sexual arousal to the male somatotype (Freund, 1985).

Age at time of clinical presentation or treatment can be helpful in deciding whether MtF transsexuals who claim to be sexually attracted to men are genuinely homosexual. Blanchard, Clemmensen, and Steiner (1987) reported that the average age at which homosexual MtF transsexuals sought treatment was about 26 years, versus about 34 years for nonhomosexual transsexuals. Nearly two decades later, Smith, van Goozen, Kuiper, and Cohen-Kettenis (2005) reported very similar figures: Homosexual MtF transsexuals sought treatment at an average age of about 28 years, versus about 37 years for nonhomosexual MtF transsexuals. Consequently, it is reasonable to assume that MtF transsexuals who transition in their mid-30s or later are unlikely to be genuinely homosexual.

With this information in mind, consider the six MtF transsexuals, T1-6, in the Zhou/Kruijver studies; descriptions of sexual orientation in quotation marks are from Zhou et al. (1995), p. 70:

- T1 was described as "male-oriented," but began hormone therapy at age 42. In light of her age, she was probably a nonhomosexual transsexual.
- T2 was described as "female-oriented" and therefore would be considered nonhomosexual in Blanchard's typology; this is consistent with her having begun hormone therapy at age 35.
- T3 was described as "female-oriented" and therefore would be considered
nonhomosexual in Blanchard’s typology; this is consistent with her having begun hormone therapy at age 36.

- T4 was described as oriented toward "both" [males and females] and therefore would be considered nonhomosexual in Blanchard’s typology; this is consistent with her having begun hormone therapy some time in her early 30s.
- T5 was described as "female-oriented" and therefore would be considered nonhomosexual in Blanchard’s typology; this is consistent with her having begun hormone therapy at age 40.
- T6 was described as "male-oriented," but began hormone therapy at age 35. In light of her age, she was probably a nonhomosexual transsexual, although this is less clear than in the case of T1.

Consequently, even if the Zhou/Kruijver findings turn out to be correct, they are not incompatible with Blanchard’s typology, because they probably describe BSTc volume and neuron number only in nonhomosexual MtF transsexuals.

**The mostly likely explanation: The Zhou/Kruijver findings reflect the effects of feminizing and masculinizing hormone therapy**

The Zhou/Kruijver findings most probably reflect the effects of transgender hormone therapy. It has been known for years that changes in androgen levels during adulthood can change the volume of sexually dimorphic brain nuclei in the expected direction in experimental animals (Cooke, Tabibnia, & Breedlove, 1999). Changes in hormone levels in adult transsexuals plausibly can have similar effects on sexually dimorphic brain structures.

A recent study by Hulshoff Pol et al. (2006) demonstrated the profound effect of transgender hormone therapy on brain volume in transsexuals: In eight MtF transsexuals treated for 4 months with ethinyl estradiol and CPA, total brain volume and hypothalamic volume decreased significantly with hormone therapy, based on pre- and post-treatment MRI studies. In a control group of nine untreated nontranssexual men, total brain volume and hypothalamic volume increased slightly over a similar period. In six FtM transsexuals treated for 4 months with testosterone, total brain volume increased and hypothalamic volume remained unchanged, whereas in a control group of six untreated nontranssexual women, total brain volume remained unchanged and hypothalamic volume decreased. Hulshoff Pol et al. wrote:

> The findings suggest that treatment of MFs with estrogens and antiandrogens decreases the male brain size toward female proportions, whereas treatment of FMs with androgens (not substantially affecting circulating estrogen levels) increases the female brain size toward male proportions. The magnitude of this change (i.e., 31 ml over a 4-month period) is striking, since it signifies a decrease in brain volume, which is at least ten times the average decrease of about 2.5 ml a year in healthy adults. . . The total brain volume changes are at least in part due to changes in medial brain structures surrounding [the] ventricles (including, but not limited to, the hypothalamus . . .). (pp. S110-S111)

Not surprisingly, Hulshoff Pol et al. (2006) conjectured that cross-sex hormone therapy might have been responsible for the Zhou/Kruijver findings:

> The bed nucleus of the stria terminalis of the hypothalamus, larger in males than in females, was found to be of female size in six MFs and of male size in one FM. All these transsexuals had received cross-sex hormone treatment before their brains were studied. Therefore, the altered size of the bed nucleus of the stria terminalis could have been due to the exposure of cross-sex hormones in
adult life. (p. S108)

As Hulshoff Pol et al. (2006) noted, all six MtF transsexuals and the one FtM transsexual had received cross-sex hormone therapy. All the MtF transsexuals had been treated with estrogen and CPA for between 7 and 13 years, except for T4, whose exact duration of hormone treatment was unknown, but was estimated to have been 5 years or more. Hormone treatment apparently continued until death in T1, T4, and T6, until three months before death in T3 and T5, and until 15 months before death in T2. All the MtF transsexuals had also undergone orchiectomy except T4, who was observed to have "significant" testicular atrophy (Kruijver et al., 2000, p. 2040). The FtM transsexual had received injectable testosterone for over 20 years, but this treatment ended 3 years before death; ovariectomy had been performed 23 years before death.

The MRI studies that Hulshoff Pol et al. (2006) conducted measured only the volume of brain structures, not neuron number. The authors argued, however, that steroid-related changes in neuron number were probably partly responsible for the volume changes they observed:

We know that sex steroids have much in common with neurotropins. For instance, like neurotropins, they regulate cell death. Indeed, the most important mechanism by which steroid hormones alter neuron number in sexually dimorphic regions is by influencing cell death. . . . Thus, our reported volume changes in the brains of transsexuals following cross-sex hormone treatment may represent alterations in neuronal cell numbers. (p. S113)

Zhou et al. (1995) were clearly mistaken when they suggested that "the small size of the BSTc in male-to-female transsexuals cannot be explained by adult sex hormone levels" (p. 70), as were Kruijver et al. (2000) when they concluded that "hormonal changes in adulthood did not show any clear relationship with the BSTc . . . neuron number" (p. 2039). On the contrary, it now seems probable that estrogen treatment was responsible for the low mean BSTc volume and neuron number observed in the six MtF transsexuals studied and that testosterone treatment was responsible for the high BSTc volume and neuron number observed in the one FtM transsexual studied.

A significant weakness of the Zhou/Kruijver studies was the inclusion of only a few nontranssexual persons with elevated cross-sex hormone levels. This may partly explain why the Zhou/Kruijver investigators underestimated the potent effects of hormone treatment on the adult brain. Contrary to a popular misconception, the Zhou/Kruijver studies did not examine any nontranssexual men who had been treated with estrogen (for example, for prostate cancer) or any nontranssexual women who had been treated with testosterone. They did examine one woman, S1, in whom a virilizing adrenal tumor had produced elevated testosterone levels and one man, S2, in whom a feminizing adrenal tumor had produced elevated estradiol levels. Neither individual had BSTc volumes or neuron numbers that were atypical for their sex, but it is probable that their cross-sex hormone levels, although elevated, had not been high enough and had not lasted long enough to be equivalent to the 5-20 years of cross-sex hormone therapy that the transsexuals had received.

Summary and conclusions

The brain-sex theory of transsexualism has never been easy to reconcile with clinical reality: Homosexual and nonhomosexual MtF transsexualism are so different clinically that it is almost impossible to imagine that they could have the same etiology. Nevertheless, for a time the Zhou/Kruijver data gave the brain-sex theory a certain superficial plausibility. In
2002, Chung et al. reported new data that raised serious doubts about the brain-sex theory, but the authors were able to explain why the theory might still be plausible. The new data reported by Hulshoff Pol et al. in 2006 did not invalidate these explanations, but it rendered them largely irrelevant. The simplest and most plausible explanation of the Zhou/Kruijver findings is that they are attributable, completely or predominantly, to the effects of cross-sex hormone therapy administered during adulthood. There is no longer any reason to postulate anything more complicated.

The brain-sex theory was never helpful in explaining clinical observations; now it has become irrelevant to explaining neuroanatomical observations. It is time to abandon the brain-sex theory of transsexualism and to adopt a more plausible and clinically relevant theory in its place.

Notes

1 Lesur, Gaspar, Alvarez, and Berger (1989) observed that the BST lies at the junction of the amygdala, the septum, and the hypothalamus. As a matter of fact, the topographical position of the BST . . . has given rise to some debate as to which [brain] system it should be included in. In rodents, it has been considered as part of the amygdala, the septum, the hypothalamus, or even the ventral striatum, according to whether the emphasis was put upon topographical relationships, connections, or cytoarchitectonic and chemoanatomic structure. (p. 181)

Alheid (2003) considered the BST to be part of the "extended amygdala," while Swaab (2003) and Byne (2007) considered it to be part of the hypothalamus. I will use the latter description for convenience, while recognizing that the issue remains controversial.

2 At the time, Swaab and Fliers (1985) and Hofman and Swaab (1989) referred to this nucleus as the "sexually dimorphic nucleus of the preoptic area."

3 Because many of the supposedly homosexual MtF transsexuals in the Smith et al. (2005) study were probably nonhomosexual (see Lawrence, 2008), the average age at which the genuinely homosexual MtF transsexuals sought treatment is probably considerably less than 28 years.

4 Attributing the BSTc findings in the MtF and FtM transsexuals to cross-sex hormone therapy does not, of course, explain the low BSTc neuron number observed in the supposedly untreated gender dysphoric male, S7. Either his advanced age (84 years) or undisclosed hormone use might have contributed to this finding. In any event, a single case means very little; Kruijver et al. (2000) found two non-gender-dysphoric men in their control group who had BSTc neuron numbers almost identical to that of S7.

5 S1 had a virilizing tumor for "at least 1 year" (Kruijver et al., 2000, p. 2039) and had a serum testosterone level as high as 26.8 nmol/L. This level is within the male normal range but is probably substantially lower than the peak testosterone levels achieved by most FtM transsexuals using injectable testosterone. S2 had a feminizing tumor for "at least 1 year" (Kruijver et al., p. 2039) and his "highest serum estradiol levels before death varied between 577-779 pmol/L" (Kruijver et al., p. 2039). This level is within the female normal range but is probably lower than the peak estradiol levels achieved by many MtF transsexuals using oral estrogen. Moreover, for both S1 and S2, the apparently limited duration of their elevated cross-sex hormone levels may have been more salient than whatever maximum hormone levels they experienced. The time periods during which S1
and S2 experienced elevated testosterone and estradiol levels were not specified by the Zhou/Kruijver investigators and might not have been known to them.

References


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