



Biological correlations in the development of diverse gender identities: a synopsis

In 2011, the World Professional Association for Transgender Health (WPATH) issued new standards of care for the treatment of trans and other gender nonconforming, people. These state that:

"The expression of identities that are not stereotypically associated with one's assigned sex at birth, is a common and culturally-diverse human phenomenon that should not be judged as inherently pathological or negative".¹

In May 2013, the World Health Organization's Executive Board received a Report by their Secretariat which, in relation to gender identity, recommended: *"abandoning a psycho-pathologising model...in favour of a model that reflects current scientific evidence and best practice..."*² That scientific evidence increasingly points to biological factors being critical to the development of gender identity.

These quotes indicate a turning point in the understanding of the diversity of gender expressions that reflect a person's identity, rather than meeting the cultural expectations for their assigned sex. Identities that are not congruent with sex-assignment are many and varied; they may be binary (man or woman), non-binary (somewhere on a spectrum between identifications as men or women), and occasionally non-gender (identification that is not associated with gender at all).

The personal experience of this incongruence may be associated with distress, described as gender dysphoria. The distress may arise from more than one factor: a persistent discomfort with the physical sex characteristics and, additionally, with the social gender role, since this is imposed, whether intentionally or inadvertently, in line with the sex assigned at birth. The distress may be intensified by social interactions that do not acknowledge the gender identity of the person, such as the use of inappropriate names and pronouns.

¹ World Professional Association for Transgender Health, Standards of Care, version 7 (2011), available at <http://www.wpath.org/documents/Standards%20of%20Care%20V7%20-%202011%20WPATH.pdf>www.who.int/classifications/

² WHO 'Improving the health and well-being of lesbian, gay, bisexual and transgender persons', May 2013, Report to the Executive Board. It is the intention of the WHO to follow the recommendation to move 'transsexualism' to a new classification (possibly 'Z'), to rename it 'gender dysphoria' or 'gender incongruence', and to change the description.

It is inevitable, therefore, that outcomes will be affected, not only by individual circumstances, but also by cultural norms and mores. For instance, it is postulated that in cultures where greater allowance is made for gender expression that is less distinctly either masculine or feminine, the discomfort and associated psychological distress of those experiencing gender dysphoria, is lessened (Connolly, 2003).³

Given the variety of gender identities and expressions, many of which do not lead to a permanent transition of the gender role, nor necessarily require medical treatment, it is almost certain that etiological pathways will also vary from individual to individual. No single route in the development of gender diversity is likely to be found. A combination of genetic, hormonal, and environmental factors impinge on the pre-natal sex differentiation of genitalia, gonads and, importantly, the brain. The biological evidence demonstrating correlations between brain development and the unique personal identity of all human beings emerges from a variety of scientific studies. A wide, although not exhaustive, review of literature relevant to atypical gender development was undertaken in 2006 (GIRES et al., 2006)⁴ and further studies have continued to emerge.

In order to understand the factors that are influential in shaping gender identity, it is helpful to consider the histories of conditions associated with genetic and hormonal anomalies, leading to ambiguous genitalia (neither clearly male nor female) in new-born infants. These babies, in common with those who suffer accidental damage to the penis neo-natally, may be subject to decisions made by doctors and, under their instruction, parents, as to whether to raise a child as a boy or a girl. In the past, faced with such anomalies or accidents, parents almost always accepted the medical viewpoint that early 'corrective' surgery – usually to create a female appearance, followed by raising the child as a girl – would deliver a congruent gender identity despite, in many cases, the underlying XY (male) karyotype. However, the reality was that some identified as boys/men. Their gender identity resolved independently of their imposed female genital appearance and feminine gender role, despite the persuasive power of these two factors. (Diamond and Sigmundson, 1997; Kipnis and Diamond, 1998; Reiner, 2004; Hines, 2004; Dessens, 2005; Ochoa, 1996)^{5,6,7,8,9,10} These

³ Connolly, P., Transgendered Peoples of Samoa, Tonga and India: diversity of psychosocial challenges, coping, and styles of gender reassignment. Paper presented at the *Harry Benjamin International Gender Dysphoria Association Conference*, Ghent, Belgium. September 10–13 (2003).

⁴ GIRES et al. (2006) Atypical gender development – a review. *International Journal of Transgenderism* 9(1):29–47. Available at www.gires.org.uk/genderdev.php

⁵ Diamond, M and Sigmundson HK (1997) Sex reassignment at birth. Long term review and clinical implications. *Archives of Pediatrics and Adolescent Medicine* 151: 298-304.

outcomes provide evidence that pre-natal sex hormones (Bao and Swaab, 2011)¹¹ and/or direct genetic effects, (Dewing et al. 2003)¹² have an indelible impact on the brain, and the formation of the gender identity. Given the greater understanding of the impact of these biological factors on the development of identity, neo-natal surgical intervention is now much less common. Indeed, many regard it as unethical since informed consent cannot be given, and congruent outcomes cannot be guaranteed (Giordano, 2012).¹³

It appears also to be the case for trans people, that their gender identities – which are not congruent with the assigned sex – are resistant to normative social pressures. It is therefore postulated that divergent brain development in the fetus is the most likely trigger for this dissonance.

Other factors, such as parenting, have been examined but correlations between parenting and gender nonconformity, have not been found (Diamond et al. 2013; Stevens et al. 2002; Zucker and Bradley, 1995; Buhrich and McConaghy, 1978).^{14,15,16,17}

⁶ Kipnis K and Diamond M. (1998) Pediatric ethics and the surgical assignment of sex. *Journal of Clinical Ethics*, 9(4) :398-410.

⁷ Reiner, WG (2004) Psychosexual development in genetic males assigned female: the cloacal exstrophy experience. In *Child and Adolescent Clinics of North America (Sex and Gender)* Milton Diamond and Alan Yates (eds.) WB. Saunders, Philadelphia 13(3): 657–674.

⁸ Hines, M (2004) *Brain Gender*, New York, Oxford University Press. A very small minority of female individuals with congenital adrenal hyperplasia, who have been raised as girls, choose to live in adulthood as males (estimates range from about 1% to about 3%).

⁹ Dessens, AB, Froukje, ME, Slijper, FME, Stenvert, LS, Drop SLS (2005) Gender dysphoria and gender change in chromosomal females with congenital adrenal hyperplasia. *Archives of Sexual Behavior* 34(4):389–397. Dessens found a much higher frequency of individuals within this group who identify comfortably as men: Of 250 raised as girls, 13(5.2%) experienced FtM gender dysphoria; of 33 raised as boys, 4 experienced MtF gender dysphoria; therefore, it appears that of the total 283, 42 individuals must be living comfortably as men or uncomfortably as women. Caveat: these figures do not represent the whole XX, CAH population.

¹⁰ Ochoa, B (1996) Trauma of the External Genitalia in Children: Amputation of the Penis and Emasculation, *Journal of Urology*, 1116.

¹¹ Bao, A-M, Swaab, DF (2011) Sexual differentiation of the human brain: Relation to gender identity, sexual orientation and neuropsychiatric disorders. *Frontiers in Neuroendocrinology* 32:214–226.

¹² Dewing, P, Shi, T, Horvath, S, Vilain, E (2003) Sexually dimorphic gene expression in mouse brain precedes gonadal differentiation. *Molecular Brain Research* 118:82-90.

¹³ Giordano, S (2012) *Children with gender identity disorder*. London New York: Routledge.

¹⁴ Diamond, M (2013) Transsexuality among twins. *International Journal of Transgenderism*, 14(1):24-38.

¹⁵ Stevens, M, Golombok, S, Beveridge, M and Team, T (2002) Does father absence influence children's gender development? Findings from a general population study of pre-school children. *Parenting Science and Practice* 2, 47-60.

Studies on co-occurrences of gender dysphoria in family groups indicate that these are unlikely to be random, and the potential for a genetic link in a subset of these individuals is postulated (Green, 2000; Diamond and Hawk, 2003; Gooren et al., 2013).^{18,19,20} The comparison between monozygotic and dizygotic twins is especially informative, since the former have a much higher degree of concordance for permanent transition of the gender role, than do the latter. Thus a strong genetic influence is inferred (Bruder et al., 2008; Diamond et al., 2013).^{21,22} A genetic anomaly of repeat polymorphisms in the gene coding for the androgen receptor has been found in those who identify as women in contradiction to their male phenotype and karyotype (Henningsson et al., 2005; Hare et al., 2008).^{23,24} Individuals with this anomaly may well not respond typically to testosterone at any stage of development.



Certain chromosome anomalies, such as XXY, XYY, XXXY and so on, in those with male phenotype, are associated with a raised incidence of individuals who identify as women (Snaith et al., 1991; Diamond and Watson, 2004).^{25,26,}

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- ¹⁶ Zucker, KJ, and Bradley, SJ. (1995) *Gender Identity Disorder and Psychosexual Problems in Children and Adolescents*, New York Guilford Press.
- ¹⁷ Buhrich, N, and McConaghy, N (1978). Parental relationships during childhood in homosexuality, transvestism and transsexualism. *Australian and New Zealand Journal of Psychiatry*, 12, 103-107.
- ¹⁸ Green, R (2000) Family co-occurrence of gender dysphoria: ten sibling or parent-child pairs. *Archives of Sexual Behavior* 29:499-507.
- ¹⁹ Diamond, M, Hawk, ST. Transsexualism among twins has a high concordance for GID among monozygotic twins and a strong but lesser concordance among dizygotic twins with the effect more noticeable among males than females. Paper presented at the Harry Benjamin International Gender Dysphoria Association Symposium, Ghent, Belgium, September 10–13 2003.
- ²⁰ Gooren, LJ, Sungkaew, T. Giltay, EJ. (2013) Exploration of functional health, mental well-being and cross-sex hormone use in a sample of Thai male-to-female transgendered persons (kathoeyes), *Asian Journal of Andrology*, 15(2):280-5.
- ²¹ Bruder, CEG, Piotrowski, A, Gijsbers, AACJ, Andersson, R, Erickson, S, de Stahl, TD, Dumanski, JP. (2008). Phenotypically concordant and discordant monozygotic twins display different DNA copy-number-variation profiles. *American Journal of Human Genetics*, 82, 763-771.
- ²² Diamond, M (2013) Transsexuality among twins. *International Journal of Transgenderism*, 14(1):24-38.
- ²³ Henningsson, S., Westberg, L., Nilsson, S., Lundström, B., Ekselius, L., Bodlund, O., Lindstrom E., Hellstrand, M., Rosmond, R., Eriksson, E., Landén, M. (2005). Sex Steroid Related Genes and Male to Female Transsexualism. *Psychoneuroendocrinology* 30(7), 657-664.
- ²⁴ Hare, L, Bernard, P, Sanchez FJ, Baird PN, Vilain E, Kennedy T, Harley, VR. (2008) Androgen receptor repeat length polymorphism associated with male to female transsexualism. *Biological Psychiatry*.
- ²⁵ Snaith, RP, Penhale, S, Horsfield, P (1991) Male to female transsexual with 47 XYY karyotype. *Lancet* 337:557–558.

Additionally, low androgen levels in an XY fetus, associated with medication provided to the pregnant mother, gives rise to a raised incidence of individuals identifying as women in contradiction to their assigned male sex (Dessens *et al.*, 1999).²⁷

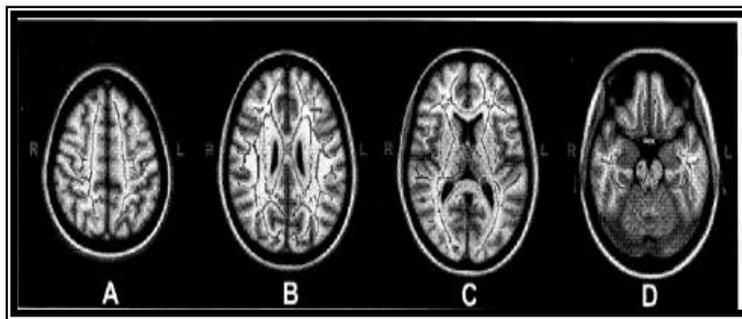
Cerebral lateralisation of hearing in the cisgender male and female populations is distinct and well-recorded. A recent study on dichotic hearing in trans individuals found that trans women's hearing is significantly different from cisgender men and, in fact, resembles the cisgender *female* pattern (Govier *et al.*, 2010).²⁸ The same study also confirmed previous studies indicating a marked correlation with non-right-handedness in both trans men and trans women (Green and Young, 2001 Zucker *et al.*, 2001).^{29,30}

Post-mortem studies, in small cohorts of trans individuals, on areas of the brain known to be sex-dimorphic, have been shown to have the potential for neural differentiation in opposition to genital and gonadal characteristics (Zhou *et al.*, 1995; Kruijver *et al.*, 2000; Garcia-Falgueras and Swaab, 2008).^{31,32,33,34} Scans of the white matter of the brains of living, untreated trans men indicate that their brains are masculinised, and have male neural patterns (Rametti *et al.*, 2011)³⁵; white matter in untreated trans women is shown to be feminised, and

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- ²⁶ Diamond, M, Watson, LA (2004). Androgen insensitivity syndrome and Klinefelter's Syndrome. In *Child and Adolescent Psychiatric Clinics of North America (Sex and Gender)*. Milton Diamond and Alayne Yates (eds); W.B. Saunders, Philadelphia 13(3):623-640.
- ²⁷ Dessens, AB, Cohen-Kettenis, PT, Mellenbergh, GJ, van der Poll, NE, Koppe, JG, Boer, K (1999). Prenatal exposure to anticonvulsants and psychosexual development. *Archives of Sexual Behavior* 28:31-44.
- ²⁸ Govier, E, Diamond, M, Wolowiec, T, Slade, C (2010). Dichotic listening, handedness, brain organisation and Transsexuality, *International Journal of Transgenderism*, 12(3) 144-154.
- ²⁹ Green, R and Young, R (2001) Hand preference, sexual preference, and transsexualism, *Archives of Sexual Behavior* 30:565-574).
- ³⁰ Zucker, K.J., Beaulieu, N., Bradley, S.J., Grimshaw, G.M., Wilcox, A. (2001). Handedness in Boys with Gender Identity Disorder. *Journal of Clinical Child Psychology and Psychiatry* 42,767-776.
- ³¹ Luders, E, Sánchez, FJ, Gaser, C, W. Toga, AW, Narr, KL, Hamilton, LS, Vilain, E (2009) Regional gray matter variation in male-to-female transsexualism, *Neuroimage*, 46(4): 904-907.
- ³² Zhou, J-N, Swaab, DF, Gooren, LJ, Hofman, MA (1995) A sex difference in the human brain and its relation to transsexuality. *Nature* 378:68-70.
- ³³ Kruijver, FPM, Zhou, J-N, Pool, CW, Hofman, MA, Gooren, LJ, Swaab, DF (2000) Male to female transsexuals have female neuron numbers in a limbic nucleus. *The Journal of Endocrinology & Metabolism* 85(5):2034-2041.
- ³⁴ Garcia-Falgueras, A and Swaab, DF (2008) A sex difference in the hypothalamic uncinate nucleus: relationship to gender identity, *Brain: a journal of neurology* 131(12):3132-3146.
- ³⁵ Rametti, G, Carrillo, B, Gómez-Gil, E, Junque, C, Segovia, S, Gomez, A, Guillamon, A. (2011). White matter microstructure in female to male transsexuals before cross-sex hormonal treatment. A diffusion tensor imaging study, *Journal of Psychiatric Research* 45 199-204.

significantly different from both male and female controls (Rametti *et al.*, 2011).³⁶

Considered in the context of the other research, cited above, these brain studies support the paradigm that the neurobiology of the brain is an important element in the development of gender dysphoria (Zhou *et al.*, 1995; Kruijver *et al.*, 2000; Garcia-Falgueras and Swaab, 2008; Rametti *et al.*, 2011; Rametti *et al.*, 2011).^{37,38,39,40,41} The continuing emergence of brain studies in trans people showing developmental differences compared with their cisgender male and female counterparts, substantiates the hypothesis that, as argued in the UK courts in 1999, they are intersexed at brain level (Gooren, 1999).⁴²



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- ³⁶ Rametti, G, Carrillo, B, Gómez-Gil, E, Junque, C, Zubiarrre-Elorza, L, Segovia, S, Gomez, A, Guillamon, A. (2011). The microstructure of white matter in male to female transsexuals before cross-sex hormonal treatment. A DTI study. *Journal of Psychiatric Research*, 1- 6.
- ³⁷ Zhou, J-N, Swaab, DF, Gooren, LJ, Hofman, MA (1995) A sex difference in the human brain and its relation to transsexuality. *Nature*, 378:68–70. This evidence was cited by Professor Louis Gooren of the University Hospital, Vrije Universiteit of Amsterdam, in his affidavit to the court in *Bellinger v Bellinger*, TLR 22-11-2000.
- ³⁸ Kruijver, FPM, Zhou, J-N, Pool, CW, Hofman, MA, Gooren, LJ, Swaab, DF (2000) Male to female transsexuals have female neuron numbers in a limbic nucleus. *The Journal of Endocrinology & Metabolism* 85(5):2034–2041.
- ³⁹ Garcia-Falgueras, A and Swaab, DF (2008) A sex difference in the hypothalamic uncinate nucleus: relationship to gender identity, *Brain: a journal of neurology* 131(12):3132–3146.
- ⁴⁰ Rametti, G, Carrillo, B, Gómez-Gil, E, Junque, C, Segovia, S, Gomez, A, Guillamon, A. (2011). White matter microstructure in female to male transsexuals before cross-sex hormonal treatment. A diffusion tensor imaging study, *Journal of Psychiatric Research* 45 199–204.
- ⁴¹ Rametti, G, Carrillo, B, Gómez-Gil, E, Junque, C, Zubiarrre-Elorza, L, Segovia, S, Gomez, A, Guillamon, A. (2010). The microstructure of white matter in male to female transsexuals before cross-sex hormonal treatment. A DTI study. *Journal of Psychiatric Research*, 1- 6.
- ⁴² Gooren LJ, University Hospital, Vrije Universiteit of Amsterdam, affidavit in *Bellinger v Bellinger*, TLR 22-11-2000.