

Dr. Luo makes a very important point regarding use of cross-gender hormone therapy (CGHT). Our review<sup>1</sup> focused on the somatic effects without mentioning the impact on the central nervous system. Our comments about insufficient research on the systemic impact of CGHT also apply to the lack of neuroanatomic and neurophysiologic research in this area. Reviews of the current state of knowledge have been published.<sup>1-3</sup> Overall, there would seem to be two main considerations to explore.

The first relates to the potential central nervous system differences in transgender individuals vs cisgender individuals prior to treatment, which may help to identify origins of gender identity and help family members understand and respond to the dysphoria of their loved ones. Research may ultimately identify anatomic loci for gender identity, sexuality, and sex. We would emphasize that the presence of differences between transgender and cisgender brains would not imply a concept of 'abnormal' vs 'normal' any more than the differences between an X chromosome and a Y chromosome.

Beyond the differences prior to initiating CGHT are those following CGHT. Dr. Luo points out that there are testosterone and estrogen receptors in the brain and that these may be stimulated or inhibited by peripherally administered hormones. Even in the periphery, the role of sex hormone receptors may influence goals of therapy. Most guidelines that provide recommendations for serum levels suggest target serum levels at the upper end of the physiological range. However, the reality is that those levels arise from cisgender individuals with specific sex hormone receptor densities. Knowledge of receptor density pre- and

post-CGHT in hormone-sensitive tissues including the brain would provide tremendous insights for treatment paradigms.

A complete and thorough understanding of transgender care will involve not only the impact of transgender hormone therapy but also the inhibition of cisgender hormones, and suppression or stimulation of hypothalamic factors and other pituitary hormones. Research is also needed on the possible roles of estrogen derivatives, progesterone, and optimal ratios of estrogen and testosterone in transwomen and transmen. Dr. Luo's final comment may ultimately need to be changed to 'Changing your sex hormones causes changes in other hormones and your brain and your body in particular ways.' Hopefully time will allow further research to fill in the gaps.

Stuart R. Chipkin, MD  
*School of Public Health Sciences,  
University of Massachusetts,  
Amherst*

<https://doi.org/10.1016/j.amjmed.2018.04.035>

## Reference

1. Mueller SC, De Cuypere G, T'Sjoen G. Transgender research in the 21st century: a selective critical review from a neurocognitive perspective. *Am J Psychiatry*. 2017 Dec 1;174(12):1155–1162 [doi:10.1176/appi.ajp.2017.17060626 Epub 2017 Oct 20].
2. Kreukels BP, Guillamon A. Neuroimaging studies in people with gender incongruence. *Int Rev Psychiatry*. 2016;28(1):120–128 [doi:10.3109/09540261.2015.1113163. Epub 2016 Jan 14].
3. Guillamon A, Junque C, Gomez-Gil E. A review of the status of brain structure research in transsexualism. *Arch Sex Behav*. 2016;45:1615–1618 [doi:10.1007/s10508-016-0768-5].

---

**Funding:** None.

**Conflict of Interest:** None.

**Authorship:** The author is solely responsible for the content of this manuscript.