

Inside the neurobiology of gender: Implications for modern physiology

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Editorial

Human biology reveals its greatest subtleties when it challenges our assumptions. Few topics exemplify this more clearly than transgender physiology, a field that compels us to revisit long-held ideas about sex, gender, and the development of identity. For physiologists, this area is no longer peripheral; it illuminates fundamental principles of endocrine regulation, neurobiology, and reproductive function, while also shaping modern clinical care. A useful starting point is clarifying the scientific distinction between sex and gender. The neurobiology of gender identity has gained considerable traction over the past two decades. Evidence suggests that several brain regions involved in body perception, identity formation, and endocrine regulation show sex-typical differentiation during fetal and early postnatal development [1]. These include the bed nucleus of the stria terminalis (BNST), hypothalamic nuclei, and cortical networks integrating sensory and emotional processing.

Postmortem and neuroimaging studies demonstrate that certain sexually dimorphic structures in transgender adults resemble the configuration typically seen in their affirmed gender. For example, the size and neuron density of the BNST in transgender women have been reported to align more closely with cisgender women than with cisgender men, irrespective of adult hormone therapy [2]. These findings, although not uniformly replicated, suggest that neural differentiation related to gender identity may diverge from peripheral genital and gonadal differentiation.

Specific investigations into cortical thickness in untreated individuals further support the notion that brain structure often aligns with gender identity rather than biological sex [3]. Functional MRI studies further show that transgender individuals often exhibit activation patterns in networks involved in self-perception, proprioception, and embodiment that differ from individuals whose gender identity aligns with sex assigned at birth [4]. This research does not imply that the brain is “male” or “female” in a simplistic sense; rather, it suggests that multiple brain circuits may organize along trajectories that contribute to one’s internal sense of gender.

Such observations reinforce an important physiological point: sexual differentiation of the brain is not a mere reflection of genital development. It is influenced by a combination of prenatal androgen exposure, local aromatization to estrogens, receptor distribution, and timing during critical neurodevelopmental windows. This layered process allows significant variation, and transgender identity may reflect one part of that spectrum.

Transgender Physiology Before Gender-affirming Therapy

Before medical transition, transgender men (assigned female at birth) typically exhibit normal ovarian function, cyclical gonadotropin secretion, and estrogen-dominant physiology. Transgender

women (assigned male at birth) possess typical testicular activity and androgen production. Recognizing this baseline physiology is critical for fertility counseling, risk assessment, and designing safe hormone protocols. The disconnect some transgender individuals experience between their physiology and identity—often intensified during puberty—highlights the importance of understanding how secondary sex characteristics influence psychological well-being. The onset of menses, voice deepening, or changes in body composition may heighten gender dysphoria, underscoring the need for physiologists and clinicians to appreciate the links between endocrine development and identity.

Hormone Therapy and Physiological Adaptation

Gender-affirming hormone therapy (GAHT) applies fundamental endocrine principles to modulate physiology in accordance with a patient's gender identity. For educators, GAHT is a powerful teaching tool. It illustrates negative feedback regulation of the hypothalamic-pituitary-gonadal axis, hormone-receptor interactions, and the systemic consequences of altering sex steroid levels. Standard clinical guidelines emphasize that these interventions require careful management to balance efficacy with safety [5].

For clinicians, understanding these mechanisms ensures safe monitoring of hematologic, cardiovascular, and metabolic parameters, especially since estrogen and testosterone each have characteristic effects on lipid profiles, coagulation pathways, and bone health. Testosterone therapy, for instance, induces specific metabolic changes that must be monitored distinct from cisgender male physiology [6]. Similarly, the use of exogenous estrogens carries specific risks regarding coagulation and acute cardiovascular events that necessitate vigilant oversight [7].

Why Physiologists Must Understand This Field

Transgender physiology is deeply relevant to postgraduate training for several reasons. Transgender physiology also exemplifies how biomedical science intersects with human rights. In India, the Supreme Court's NALSA judgment affirmed the constitutional right to gender self-identification, positioning healthcare professionals at the forefront of delivering respectful and scientifically grounded care.

Comprehensive standards of care now exist to guide professionals in creating an environment where transgender individuals receive competent and compassionate treatment [8]. Ultimately, this field invites physiology to do what it does best: illuminate complexity. It teaches that sex and gender are multidimensional, that the brain and body may follow distinct developmental trajectories, and that hormone physiology is remarkably adaptable. Far from being a niche topic, transgender physiology is a window into the broader diversity of human biology and an opportunity for the scientific community to match knowledge with empathy.

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