The neurobiology and neurocognition of gender dysphoria

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Abstract.
Background: Gender Dysphoria (GD) is a psychological distress characterized by an incongruence between an individual's internal gender identity and the sex assigned at birth. This phenomenon has gained increased attention due to its rising prevalence, particularly among adolescents in Western societies. Objectives: This narrative literature review examines the neurocognitive, neurobiological, and neurodevelopmental aspects of GD, aiming to provide insights for the assessment of transgender adults. The growing epidemiology requires an informed and inclusive medical system. Methods: Hand searches across PubMed and Google Scholar were performed to study the neurobiological and neurocognitive aspects of Gender Dysphoria. Results: Neuroimaging studies reveal distinct brain structures in transgender women compared to cisgender men, particularly in regions like the putamen, which is involved in emotions and learning. The intricate interplay of genetic, hormonal, and neurobiological factors is implicated in GD. Differences in gray and white matter volumes, cortical thickness, and brain activation patterns have been observed in individuals with GD, implying a multifactorial basis for this condition. Neuroendocrine factors, including testosterone and estrogen levels, play a role in the development of brain structures related to sexual differentiation. Genetic contributions, such as allelic variations in genes associated with sex steroid production, have also been linked to transgenderism. The findings underscore the complexity of GD and its underlying mechanisms, contributing to a deeper understanding of this phenomenon and offering insights into assessment and support for transgender individuals.

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INTRODUCTION

Gender Dysphoria is a distress experienced by individuals that causes them to identify with a sex other than the one assigned at birth. The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders has described gender dysphoria to be an incongruence between one's internal sense of gender and the gender they were assigned at birth that has lasted for at least 6 months. Epidemiology has been rising rapidly across the Western diaspora. The prevalence of GD across the adolescent population has increased substantially with about 2.3% of females and 3.6% of males reporting significant symptoms according to a replication student in Northern Europe. (1)

Recent scientific progress, attempts have been made to characterize this psychological distress to understand better, the needs of individuals who pursue a transition from the sex they were assigned at birth.

Clinicians must engage in attempts to analyze and distinguish between unique experiences and mental health symptoms to ensure accurate and ethical dissemination of healthcare, making it inclusive. The following narrative review literature will discuss the neurocognitive, neurobiological, and neurodevelopmental aspects of gender dysphoria in an attempt to offer a practical guide on how to assess transgender adults.

Neurocognitive and Neurobiological Correlates of Gender Dysphoria

There is a lot of evidence that suggests that structural and functional differences between cis and transgendered individuals are contributed by certain biological factors. Transgendered individuals have different brain structures as opposed to cis-gendered individuals. For instance, the Putamen, a major part of the basal ganglia, involved in movement, learning, and emotions was found to be either more minor (2) or larger (3) in transgender women compared to cis-gendered men and trans women having a larger volume of putamen relative to cis women (4).

Experience of gender dysphoria in transgendered individuals occurs due to these differences. Research suggests that when DTI (Diffusion Tensor Imaging) was used to
measure the white matter tracts in the brains of cis and trans-gendered men and women, it was observed that transgendered women had increased connectivity between right putamen and right insula. In contrast, trans men were observed with a decreased connectivity of the same. (5)

The insula is the region of the brain that is involved in interoception, emotions, and self-awareness. These findings could explain the neuroanatomy that corresponds to gender dysphoria.

Presentations of Gender Dysphoria were also studied to be associated with the use of lysergic acid diethylamide, further, hypothesizing the superior parietal cortical area to be associated with body image and hence, contributing to the symptoms of GD. (25)

Many theories suggest the multifactorial basis of Gender Dysphoria: genetics and neurobiological, hormonal, and psychological. Several studies have stated that the neuroanatomy physiology of a dysphoric person is different from that of a non-dysphoric one. (6) Distinct grey matter volume and brain activation and connectivity differences were found in individuals with Gender Dysphoria compared to controls, suggesting a neurobiological basis of Gender Dysphoria; which leads to the concept of brain gender. Individuals with Gender Dysphoria encounter a recurrent conflict between their brain gender and the societal feedback; which causes recurrent and ongoing cognitive dissonance, finally leading to Gender Dysphoria and functional connectivity and activation changes in the transgender brain. (7) Another study related to grey matter reveals that the bed nucleus of the stria terminalis might be involved in the control of autonomic, neuroendocrine, and behavioral responses. (8) In transsexualism this structure developed in a sex-atypical way with size and neuron number closer to the desired than that of the natal sex. (9)

A recent study analyzed grey matter volume in MtF and FtM transsexuals and control males and females and it was found that the cerebellum (anterior lobe, left posterior lobe, declive, dentate, culmen) left angular gyrus and left inferior parietal lobule, with both the MtF and FtM transsexual individuals having reduced grey matter volumes compared to
controls. (10) A study showed some areas of the grey matter of transgender individuals resemble those of control subjects who have the same gender identity. (13)

White matter

The earliest study on anatomical differences between transsexuals and control males and females mainly focused on the corpus callosum, the white matter structure connecting both cerebral hemispheres. However, there was no found evidence or major differences in shape between the sexes and between the transsexuals of either sex and control males and females. (24) However, a positive finding stated differences between the male and female shape of the corpus callosum at the midsaggital plane, and using this value of FtM and MtF transsexuals were closer to their gender identity than to their natal sex. (11) In another study diffusion-weighted magnetic resonance imaging (DW-MRI) in a sample of hormonally untreated MtF and FtM transsexuals with early-onset gender dysphoria and controls to determine the influence of biological sex, gender identity as well as sexual orientation on several diffusivity parameters. The mean diffusivity (MD, a measure of the total diffusivity within a voxel) was observed to be highest for female controls, followed by FtM transsexuals, then MtF transsexuals, and lowest for male controls. For MD values, transsexuals seem to take up an intermediate position between the sexes. No group differences were found in FA maps. Sexual orientation had no significant effect on the diffusivity parameters. (12)

Cortical thickness

Sexual discrimination can be found in cortical thickness regardless of differences in the brain and body size. An increase in cortical thickness in women compared to men was recorded in the parietal and frontal lobes, occipital, and temporal lobes. Considering this difference in cortical thickness between men and women, we could expect signs of feminization/masculinization in the context of research on transgenders. (13) Measured cortical thickness in both MtF and FtM transgenders; the cortical thickness in MtF transgenders shows signs of feminization, with a greater thickness than the male control group and specifically in areas such as the orbitofrontal occipital region, island
region, and medial region. (14)

Neuroimaging findings
In a study, neuroimaging studies were conducted to compare brain activation patterns of transsexuals and controls during a task. They measured cerebral activation patterns of positron emission tomography (PET) while smelling odorous steroids. (15) It was found that the response pattern of MtF transsexuals was found to be between that of male and female but mainly female characteristics.

In another study mainly conducted on adolescent groups it was found that the cortical structure of gender dysphoria Assigned female at birth (AFAB) adolescents aligns with the experienced gender in the context of age-related changes in sexual attractions during adolescence reflected mostly in tissue microstructure. (16)

Neuroendocrine factors
Changes in cortical thickness are known to be associated with testosterone levels in males and females. (18) A study shows that prenatal exposure to testosterone can be an etiological factor of transgenderism particularly in MtF form. (13) After the conduction of the experiment it was seen that for FtM transexuals an increase in cortical and subcortical grey matter volume after testosterone treatment. For MtF transexuals the volume decreased after treatment with oestrogen and anti-androgens. (17)

Genetic Contributions
Various studies suggest the relationship between transgenderism and genes involved in the production of sex steroids. A study has shown that CYP17 is linked with an increase in serum and plasma levels of estradiol, progesterone, and testosterone. It was observed that damage to the female allelic distribution of the CYP17 is associated with forms of FtM transgenderism and not with MtF. (19)

A recent study suggests the association with the A2 allelic frequency of the CYP 17 MspA1 polymorphism, as an allelic frequency that appears to be sex-dependent in transgenders, but not in the general population, and with a higher frequency in FtM cases, compared to that MTF. (20)

Sexual development of the brain
The fetal brain develops in the male or female direction
based on the hormonal changes in the intrauterine period. Although the development of the genitalia happens during the first 2 months of pregnancy, sexual differentiation starts in the second half of the pregnancy. This means that both these processes can be independently influenced. (21)

The development of gonads occurs before the sexual development of the brain. The primary gene that is responsible for sexual differentiation is the sex-determining region on the Y-chromosome (SRY) or testis determining factor (TDF) in males, which causes the production of testosterone and the development of male genitalia. (22)

The neural circuits pertaining to sexual differentiation develop in utero and are activated during puberty. Estrogens, progesterone, and testosterone influence the sexual differentiation of the brain.

The phenotypic sex is primarily determined by the physical state of the gonads and the secondary sexual characteristics, while the genotypic sex is determined by the SRY gene and hormonal influences in utero.

However, this still does not explain all the facets of sexual attraction and behavior during development.

Sexual identity is used to describe how an individual consciously perceives their phenotypic sex; while sexual orientation refers to the cognitive experience of emotions and attractions associated with sexual relationships, and is simply not coordinated with obvious genotypic, phenotypic, or gender-associated characteristics. Dysfunctions occurring at various levels of sexual development may lead to disorders of sexual development.

Hormone-dependent changes occur in the brain during puberty. While studies in rats have identified the anatomical basis for sexual differentiation in the brain, human studies could not find any structural basis. (23) However, subtle functional changes happen in the brain, especially the amygdala, during puberty.

Results & Discussions

The presented discussion delves into the complex interplay of biological factors that contribute to the distinct differences in both structure and function observed between cisgender individuals and those identifying as
transgender. Drawing from a range of scientific studies, the narrative outlines how transgender individuals exhibit notable variations in brain structures compared to cisgender individuals, particularly in areas like the putamen and insula. The putamen's role in controlling movement, learning, and emotions is emphasized by its differing sizes in transgender women compared to cisgender men, along with a larger volume in transgender women compared to cisgender women. The central focus of this exploration revolves around how these brain differences play a role in the experience of gender dysphoria in transgender individuals.

These differences contribute to the inner conflict of gender dysphoria, where one's internal sense of gender clashes with societal perceptions. This incongruence, fueled by the mismatch between one's brain-based gender identity and external societal norms, ultimately gives rise to the phenomenon of gender dysphoria. This multifaceted understanding is bolstered by factors like genetics, neurobiology, hormones, and psychology. Research indicates discernible distinctions in gray and white matter volumes, patterns of brain activity, and connectivity between those with gender dysphoria and those without. These disparities contribute to the concept of "brain gender," where internalized gender identity grapples with external cultural expectations.

This ongoing struggle leads to cognitive dissonance that culminates in gender dysphoria. Genetics also come into play, with studies indicating a connection between transgenderism and genes involved in sex hormone production. Particularly, certain genetic variants of CYP17 are linked to the development of gender dysphoria, especially in female-to-male cases. Looking at the developmental timeline, prenatal exposure to hormones and the hormonal changes during puberty leave a lasting impact on the brain's structure. Testosterone, estrogen, and progesterone guide the intricate process of sexual differentiation in the brain. This process imprints the core aspects of sexual identity and orientation onto the neural landscape, revealing a rich spectrum that surpasses mere physical attributes. In conclusion, this analysis delves into the nuanced interplay of biological elements...
contributing to the intricate phenomenon of transgenderism and gender dysphoria. By examining brain structures, genetics, hormonal influences, and psychological factors, we gain a deeper insight into the profound complexity of personal identity and its connection to the biological foundations of selfhood.

**Conclusion**

The literature explored the idea of concept with a scientific bias and explored various neurobiological and neurocognitive aspects and the commensurate neuroimaging to underscore the incongruence experienced by individuals. The social settings in parts of India contribute to delayed consultation in conjunction with a lack of inclusive institutions. (26, 27)

The disparities within brain structures and neurobiological patterns of transgender individuals compared to cisgender counterparts underscore the profound emotional conflict at the heart of GD. The convergence of genetic, hormonal, and neurobiological elements weaves a complex narrative that drives the experience of GD.

The brain's intricate interplay with identity and societal norms manifests in the concept of "brain gender," illuminating the cognitive dissonance that ultimately leads to GD. Genetic variants and hormonal influences add layers to this complex story, shaping one's sense of self from prenatal stages through puberty.

In conclusion, the literature attempted to explore how GD enriches our comprehension of human identity, offering insights for inclusive medical support and fostering empathy for the diverse journeys of transgender individuals.

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