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Beyond The Binary: The Effects of Gender-Affirming Hormone Therapy on Sexual Desire

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Abstract

Gender-affirming hormone therapy (GAHT) is central to transgender healthcare, yet its short-term effects on sexual desire remain insufficiently understood. This longitudinal study examined how approximately four months of high-dose GAHT influence dyadic and solitary sexual desire and hypothalamic volume in both transgender men and women.

Nineteen transgender men and ten transgender women underwent two examinations – once before GAHT initiation and once after at least 12 weeks of treatment. Each examination included a structural Magnetic Resonance Imaging session, blood sampling for the assessment of serum testosterone and oestradiol levels, and completion of the Sexual Desire Inventory. Linear mixed models tested group-specific changes in sexual desire, associations between sex steroids and desire, and moderation by twelve hypothalamic regions of interest.

GAHT produced divergent trajectories, with increases in dyadic and solitary desire in transgender men and reductions in transgender women. In transgender men, testosterone showed consistent associations with desire, whereas in transgender women oestradiol was more strongly linked to sexual desire, while testosterone showed no consistent association. Although hypothalamic volume showed no uniform treatment effect, it significantly moderated hormone-desire associations in a group- and hormone-specific manner. These findings indicate that GAHT exerts substantial, directionally distinct effects on sexual desire and suggest that hypothalamic morphology may be associated with how endocrine changes relate to motivational outcomes in the domain of sexuality.

Keywords: Gender-affirming hormone therapy (GAHT), transgender individuals, sexual desire, sex steroids, hypothalamic volume, MRI

Zusammenfassung

Geschlechtsangleichende Hormontherapie (GAHT) ist zentral für die Gesundheitsversorgung von transgeschlechtliche Personen, doch ihre kurzfristigen Effekte auf sexuelles Begehren sind bislang unzureichend verstanden. Diese longitudinale Studie untersuchte, wie etwa vier Monate hochdosierte GAHT dyadisches und solitäres Begehren sowie das hypothalamische Volumen bei transgeschlechtlichen Männern und transgeschlechtlichen Frauen beeinflussen.

Neunzehn transgeschlechtliche Männer und zehn transgeschlechtliche Frauen wurden vor Beginn der GAHT und nach mindestens zwölf Wochen Behandlung untersucht. Zu beiden Zeitpunkten wurden strukturelle Magnetresonanztomographien unternommen, Blutabnahmen zur Bestimmung der Testosteron- und Östrogenspiegel im Serum durchgeführt sowie der Sexual Desire Inventory ausgefüllt. Lineare Mehrebenenmodelle prüften gruppenspezifische Veränderungen des sexuellen Begehrens, Zusammenhänge zwischen Sexualhormonen und Begehren sowie Moderationseffekte von zwölf hypothalamischen Regionen.

GAHT führte zu divergenten Verläufen, mit Zunahmen des dyadischen und solitären sexuellen Begehrens bei transgeschlechtlichen Männern und Abnahmen bei transgeschlechtlichen Frauen. Bei transgeschlechtlichen Männern zeigten sich konsistente Zusammenhänge zwischen Testosteron und sexuellem Begehren, während bei transgeschlechtlichen Frauen insbesondere Östradiol stärker mit sexuellem Begehren verknüpft war und Testosteron keine konsistenten Zusammenhänge zeigte. Obwohl sich das hypothalamische Volumen nicht einheitlich veränderte, moderierte es die Zusammenhänge zwischen hormonellen Veränderungen und sexuellen Begehren. Die Befunde deuten darauf hin, dass GAHT erhebliche, richtungsspezifisch unterschiedliche Auswirkungen auf das sexuelle Verlangen hat, und legen nahe, dass die Morphologie des Hypothalamus damit zusammenhängen könnte, wie endokrine Veränderungen mit motivationalen Ergebnissen im Bereich der Sexualität verknüpft sind.

Schlüsselwörter: geschlechtsangleichende Hormontherapie (GAHT), transgeschlechtliche Personen, sexuelles Begehren, Sexualhormone, hypothalamisches Volumen, MRT

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Introduction

Transgender individuals experience a discrepancy between the sex assigned at birth and their gender identity. For some individuals this incongruence is accompanied by Gender Dysphoria (GD) , a clinical condition characterised by a persistent wish to live and be recognised in the affirmed gender and by gender-related distress that can interfere with everyday life and motivate the wish for gender affirming treatment (American Psychiatric Association, 2013; Beek et al., 2015; Joseph et al., 2017). Contemporary classification systems have moved away from pathologising gender diversity as such and instead emphasise distress and functional impairment as the focus of diagnosis, with GD in the DSM-5 and Gender Incongruence in the ICD-11 providing diagnostic frameworks that are intended to reduce stigma while safeguarding access to care (American Psychiatric Association, 2013; World Health Organization, 2019). Against this backdrop, understanding how gender-affirming intervention affect different aspects of health and wellbeing remains a central task for clinical research and practice.

Gender-affirming hormone therapy (GAHT) is a cornerstone of the medical transition process for transgender men (TM) and transgender women (TW). It involves the administration of sex hormones, inducing bodily changes that more closely align with the experienced gender, thereby relieving gender-related distress (Coleman et al., 2012; Hembree et al., 2017). Guidelines issued by international expert groups emphasise its essential position in transgender healthcare, offering specific recommendations on indications and monitoring (Coleman et al., 2012; Hembree et al., 2017). Beyond somatic effects (Hembree et al., 2017; Unger, 2016), GAHT has been associated with reductions in GD, body dissatisfaction as well as improvements of quality of life (Fisher et al., 2016; Van Leerdam et al., 2023). However, sexual health remains a comparatively understudied domain. Sexual desire is a central component of well-being, understood as a dynamic motivational state shaped by biological, psychological, and interpersonal factors, which can be differentiated into dyadic and solitary desire (Carvalho & Nobre, 2010; Spector et al., 1996). For transgender individuals, sexual desire should be considered in the context of medical transition, during which hormonal and bodily changes may alter sexual desire. GAHT provides a unique opportunity to examine the impact of endocrine changes on sexual desire. Existing longitudinal studies indicate that GAHT can substantially alter sexual desire in both TM and TW, but findings are mixed and particularly heterogeneous in TW (Defreyne et al., 2020; Van Dijk et al., 2019). The hypothalamus is a key structure in networks that integrate hormonal and motivational signals, and neuroimaging studies indicate that GAHT can alter its volume in transgender individuals (Cacioppo, 2017; Konadu et al., 2023a; Kranz et al., 2018; Pol et al., 2006). The present study aims to address these gaps by

examining sexual desire in TM and TW during the first months of high-dose gender-affirming hormone therapy, and by relating changes in desire to alterations in testosterone and oestradiol levels, as well as to hypothalamic volume. By integrating hormonal, neurostructural and psychological measures, the study seeks to clarify how endocrine and neural factors jointly shape sexual desire through GAHT.

Theoretical Background

Terminology

In recent years, there has been a considerable refinement of the terminology concerning sex and gender. The aim is to provide explicit, non-pathologising definitions and reduce conceptual conflation (Skordis et al., 2020) underscoring the need for terminological precision and consistency.

Biological sex refers to chromosomal, hormonal, and anatomical determinants, most commonly reflected in a 46, XX chromosomal complement in females or 46, XY in males, as well as corresponding reproductive structures (Shumer et al., 2016; Skordis et al., 2020). In contrast, gender identity describes an individual's inner sense of self in relation to gender; this may involve identifying as male, female, both, neither or anywhere along a non-binary spectrum (Shumer et al., 2016). Gender expression (also known as gender presentation) is the outward manifestation of gender through appearance, behaviour, clothing, and other social cues, and it is shaped by cultural and societal norms (Shumer et al., 2016; Skordis et al., 2020). It is equally important to distinguish gender identity from sexual orientation. Sexual orientation refers to patterns of sexual or romantic attraction (e.g. heterosexual, homosexual, bisexual, pansexual or asexual) and is conceptually independent of gender identity (Shumer et al., 2016).

The terms cisgender and transgender provide important distinctions. Cisgender describes individuals whose gender identity is congruent with the sex assigned at birth, while transgender serves as an umbrella term for individuals whose gender identity differs from their assigned sex (Cooper et al., 2020; Shumer et al., 2016). Introduced by psychiatrist John Oliven in 1965, the term transgender came to be used as an umbrella term by the late 1990s, gradually supplanting the term transsexual, which had primarily been applied to individuals pursuing surgical transition (Williams, 2014). This shift foregrounds gender identity rather than the physical appearance of sex. To date, most studies have focused on TW, individuals that were assigned male at birth but identify as female and TM, who were assigned female at birth but identify as male (Nguyen et al., 2019).

As briefly outlined in the Introduction, being transgender is often, though not invariably, associated with GD – a potentially disabling condition characterized by distress arising from a discrepancy between a person's sex assigned at birth and their gender identity (American Psychiatric Association, 2013). GD has been linked to elevated rates of self-harm, suicidality and functional impairment (Beek et al., 2015; Hartig et al., 2022; Joseph et al., 2017). Another highly relevant term in this context is transition, which refers to the process by which an individual begins to live and present in accordance with their gender identity (Bouman & Arcelus, 2017). Some individuals alleviate their GD through social transition involving a change of name, gender expression and/or gender role. Others seek gender-affirming medical interventions, such as GAHT and/or surgical procedures to bring their physical characteristics into alignment with their gender identity and thereby alleviate symptoms of GD (Coleman et al., 2012).

In line with contemporary, non-pathologising usage, this study uses the term transgender throughout.

Classification: Gender Dysphoria and Gender Incongruence

The current diagnostic landscape is defined by two complementary systems, the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) and the *International Classification of Diseases* (ICD). These systems classify gender-related diagnoses differently, but both aim to reduce stigma and ensure access to care.

The American Psychiatric Association published the fifth and current edition of the DSM in 2013 (American Psychiatric Association, 2013). The DSM is the handbook used by clinicians and psychiatrists to classify and diagnose mental conditions. Within the DSM-5, GD is defined as clinically significant distress or impairment associated with a marked incongruence between an individual's experienced gender and their sex assigned at birth (American Psychiatric Association, 2013). The clinical target is the distress rather than the identity itself, reflecting an explicit effort to avoid pathologising gender diversity (Shumer et al., 2016; Zucker et al., 2013). The DSM-5 locates GD in a section separate from paraphilic disorders and sexual dysfunctions and specifies separate criteria for both, children, adolescents and adults. Key diagnostic criteria include persistent incongruence alongside strong desires related to live and be recognised as the experienced gender, and where relevant, to modify primary or secondary sex characteristics. This must have lasted for at least six months and be associated with functional impairment. It is important to distinguish between transgender people who experience distress and those who do not, because a diagnosis of GD requires clinically significant distress or functional

impairment (Coleman et al., 2012; Corneil et al., 2010). The *International Classification of Diseases* (ICD), published by the World Health Organization (WHO), is a universal diagnostic system that standardises disease coding. It facilitates the collection of mortality and morbidity statistics, as well as the exchange of information among health systems, policymakers, insurers, and researchers. In the ICD-11 (effective 1st January 2022), Gender Incongruence is defined as a marked and persistent incongruence between experienced gender and assigned sex, often accompanied by a wish to transition socially and/or medically in order to live and be recognised in the experienced gender (World Health Organization, 2019). According to the ICD-11, distress is not required for diagnosis, and incongruence alone may warrant access to gender-affirming and supportive interventions. In line with the depathologisation of gender diversity, Gender Incongruence has been moved from the ICD-10 chapter on *Mental and Behavioural Disorders* to the ICD-11 chapter *Conditions related to sexual health*, thereby removing the diagnosis from the mental disorders section while preserving administrative pathways for treatment and reimbursement (Dhejne et al., 2016; Drescher, 2014; Richards et al., 2015).

Both frameworks can accommodate non-binary identities for clinical use, provided that the assessment and documentation processes remain responsive to the individual's goals.

In addition to the categorical diagnoses found in DSM-5 and ICD-11, GD and Gender Incongruence are mostly assessed using dimensional self-report questionnaires. These instruments assess the intensity and frequency of gender-related distress or incongruence and are more commonly used in clinical screening. They differ in terms of their target population, conceptual focus (e.g. distress, incongruence or body dissatisfaction), time frame and response format. Table 1 provides an overview of established self-report scales and their key characteristics.

Table 1: Overview of selected self-report instruments used to assess Gender Dysphoria or Dender Incongruence.

Scale Name/ Abbreviation	Type	Target Population	Key Features
Utrecht Gender Dysphoria Scale (UGDS)	self-report	Adolescents & Adults	12 items, 5-point Likert, timeframe not specified
Utrecht Gender Dysphoria Scale- Gender Spectrum (UGDS-GS)	self-report	Adolescents & Adults	18 items, 5-point Likert, timeframe not specified
Gender Identity/Gender Dysphoria Questionnaire for Adolescents and Adults (GIDYQ-AA)	self-report	Adolescents & Adults	27 items, 5-point responses, past-12-months timeframe
Gender Preoccupation and Stability Questionnaire (GPSQ/GPSQ-2)	self-report	Adolescents & Adults	14 items, 5-point scale (0-4), past-two-weeks timeframe
Kiel Gender Dysphoria Questionnaire (KGDQ)	self-report	Adults (18+)	26 items, 5-point Likert, past-4-weeks timeframe
Transgender Adolescent Stress Survey-Dysphoria (TASS-D)	self-report	Adolescents (12-17)	Two subscales: Body-Related Distress & Gender Expression, item-endorsement (yes/no) plus 0-10 distress rating, timeframe not specified

Note. Overview of selected self-report instruments used to assess Gender Dysphoria or Dender Incongruence. The table summarises the main conceptual focus, target population, number of items, response format and specified time frame of each scale. The instruments are based on the following original publications: UGDS: (McGuire et al., 2020); UGDS-GS: (Schneider et al., 2016); GIDYQ-AA: (Deogracias et al., 2007); GPSQ-2: (Bowman et al., 2024); KGDQ: (Möck et al., 2025)*; TASS-D: (Schrager et al., 2024).*

History

Although the term transgender is relatively recent, psychiatric and medical thinking about what would later be called transsexualism, and more broadly transgender phenomena, took shape in the late nineteenth and early twentieth centuries (Drescher, 2014). By the 1920s Magnus Hirschfeld had distinguished gender variance from same-sex desire, and he popularised the term *transsexual*. He also referred patients for surgical interventions at the Institut für

Sexualwissenschaft in Berlin Harry Benjamin later systematised clinical responses in *The Transsexual Phenomenon* (Benjamin, 1967), helping to establish pathways for hormonal and surgical care that influenced subsequent practice. The first gender-related diagnosis to appear in a diagnostic classification systems was *Transsexualism* in the class of psychosexual disorders in DSM3- in 1980 (American Psychiatric Association, 1980). The DSM-3 also listed *Gender Identity Disorder of Childhood* and *Atypical Gender Identity Disorder*. The DSM-4 published in 1994, combined this terminology as *Gender Identity Disorder* (American Psychiatric Association, 1998; Beek et al., 2015). In the DSM-5 (2013), the nomenclature shifted to *Gender Dysphoria*, with the diagnosis placed in its own section, apart from paraphilic disorders and sexual dysfunctions. This reflects a broader effort to reduce stigma while maintaining workable routes to treatment and evaluation (American Psychiatric Association, 2013; Drescher et al., 2012; Shumer et al., 2016; Zucker et al., 2013). In the WHO system, ICD-10 classified Transsexualism under Mental and Behavioural Disorders (World Health Organization, 2009). Over the following decades, scholarly debate addressed whether incongruence between experienced gender and assigned sex should be conceptualised as a natural variation or as a disorder, and how diagnostic placement influences stigma, discrimination, and access to care (Dhejne et al., 2016; Meyer-Bahlburg, 2010). In response, expert working groups proposed replacing the term transsexualism with Gender Incongruence and the relocation of the category from the mental disorders chapter to a chapter concerned with sexual health. The ICD-11 adopted the term Gender Incongruence, with the revision taking effect on 1 January 2022 (Dhejne et al., 2016; Drescher et al., 2012; Richards et al., 2015; World Health Organization, 2019). Taken together, the changes suggest an ongoing commitment to advancing depathologisation while ensuring prompt access to gender-affirming care. The placement and wording of categories have moved across both classification traditions in response to evolving clinical evidence, community input and ethical considerations. The work of early clinical pioneers such as Hirschfeld and Benjamin provided a foundation for medical responses, and contemporary revisions in the DSM-5 and ICD-11 demonstrate a sustained effort to align diagnostic terminology with current knowledge and with the aim of minimising stigma while ensuring access to care remains unhindered (Beek et al., 2015; Drescher et al., 2012; Shumer et al., 2016; Zucker et al., 2013).

Epidemiology

According to published reports, the prevalence of GD is highly variable. Estimates depend strongly on definitions, sampling frames, and measurement strategies, as well as on whether studies are based on clinical records or population surveys.

In the DSM-5, the reported prevalence in adults assigned male at birth ranges from 0.005% to 0.014%, and from 0.002 to 0.003% in those assigned female at birth (American Psychiatric Association, 2013, p. 454). However, these values are considered conservative as they are derived from specialist treatment settings and exclude individuals who do not seek care (Skordis et al., 2020). By contrast, survey-based studies that rely on self-identification typically report larger proportions. A review of recent survey data suggests that approximately 0.5-1.3% of children, adolescents, and adults self-identify as transgender (Zucker, 2017). In the United Kingdom, survey data similarly indicate an overall proportion of about 0.5% among adults (Winter et al., 2016). In line with this pattern, a United States analysis revealed that approximately 0.6% of adults identify as transgender when a binary self-identification item is employed (Flores et al., 2016). In contrast, diagnosis-based meta-analyses report far lower numbers, for example 0.0068% (Collin et al., 2016), reflecting restrictive case definitions and incomplete data from outside specialist services. To avoid the use of pathologising language and to recognise that transgender identity does not have a specific onset time in an epidemiological sense, some authors recommend referring to numbers and proportions rather than incidence and prevalence (Adams et al., 2017; Bouman et al., 2017).

Across Europe and North America, clinics report sustained increases in assessments and referrals (Fielding & Bass, 2018; Shumer et al., 2016). It is estimated that the number of people seeking related care increases by about 18% each year, (Fielding & Bass, 2018), although the precise rate varies by setting and period (Bouman et al., 2016). Proposed explanations for this trend include greater visibility, wider access to information through online and community channels, campaigns for rights and reduced discrimination, increased awareness among professionals, and improvements in referral routes and service organisation (Bouman et al., 2016; Coleman et al., 2012; Keuzenkamp & Kuyper, 2013; Wylie et al., 2016). Media discussion may also facilitate earlier and more open self-identification, although the authors caution that transgender individuals remain at a higher risk of victimisation, suicidality, and economic disadvantage, factors that influence both survey participation and access to care (Joseph et al., 2017).

Sex steroid hormones

This chapter considers how GAHT interventions exert their effects through the biological pathway of sex hormones. There are three major classes of sex steroid hormones: androgens, oestrogens and progestogens. The present section focuses on oestrogen and testosterone as these are the hormones most commonly targeted in GAHT. These steroids are synthesised from cholesterol in the gonads and the adrenal cortex and are further shaped by local conversion in target tissues (Pillerová et al., 2021).

Across human development sex steroids organise and shape the body and mind in a stage-specific manner (Berenbaum & Beltz, 2011). During prenatal development, testicular androgens including dihydrotestosterone, are responsible for the masculinisation of the Wolffian derivatives and the external genitalia. Meanwhile, anti-Müllerian hormone induces regression of the Müllerian ducts, while testicular androgens support the development of Wolffian derivatives; in the absence of these signals, development follows the typical female pathway (Hiort, 2013). In the early stages of infancy, a brief period of mini puberty activates the hypothalamic-pituitary-gonadal axis, resulting in penile and testicular growth in males, and transient activation of the ovaries and breast tissue in females (Kuiri-Hänninen et al., 2014).

During puberty, oestrogen and testosterone drive growth and skeletal maturation. Oestradiol is essential for epiphyseal closure in both sexes; testosterone contributes to pubertal growth in males, largely via aromatisation to oestradiol, while oestradiol promotes maturation of the ovaries and uterus in females. Meanwhile, testosterone promotes penile and testicular growth, as well as androgen-dependent development of pubic hair (Clark & Rogol, 1996; Frank, 2003; Klein et al., 1996; Luo et al., 2024; Mauras, 2001).

In adulthood, testosterone supports muscle and fat free mass and sexual function, while oestradiol is central to bone remodelling in both women and men (Bhasin et al., 1996; Khosla et al., 2012). Later in life, oestradiol decline after menopause is linked to increased visceral adiposity and accelerated bone loss, whereas men show gradual testosterone decline alongside higher fat mass and lower lean mass (Harman et al., 2001; Lovejoy et al., 2008). These declines in sex steroids are also associated with an increased risk of cardiovascular disease, changes in memory and mood, and features of immune ageing, such as greater chronic inflammation (Barth et al., 2023; Fontaine et al., 2025; Giefing Kröll et al., 2015; Janowsky et al., 2000).

Testosterone is aromatised to oestradiol and reduced to the non-aromatisable androgen dihydrotestosterone by 5-alpha-reductase. This occurs within a regulatory context provided by the hypothalamic-pituitary-gonadalaxis and its pulsatile control of luteinising hormone and follicle-stimulating hormone (Celotti et al., 1997; Wierman, 2007).

Beyond reproduction, oestrogen and testosterone influence neurotransmitter levels and receptors, as well as the architecture and function of neural and glial cells in cisgender individuals. This situates these hormones as broad modulators of central nervous system function rather than signals confined to sexual differentiation alone (Nguyen et al., 2019).

During the prenatal, perinatal and peripubertal windows, sex steroids organise brain morphology and subsequent responsiveness. There is strong evidence that oestrogen influence apoptosis, cell survival, neurite growth and synaptic connectivity. However, the specific organisational roles of oestradiol and testosterone in the human brain and in psychosexual differentiation remain a matter of debate (Baum & Bakker, 2017; Cooke et al., 1998; McCarthy, 2008; Schulz & Sisk, 2016). In adulthood, the activational effects are generally non-permanent yet measurable. Pharmacological and imaging studies in humans demonstrate structural, functional and neurochemical alterations that can be detected using functional and structural magnetic resonance imaging (MRI) and positron emission tomography (PET). These alterations have behavioural and emotional correlates, such as mood variations across the menstrual cycle (Jovanovic et al., 2009; Pletzer et al., 2018; Syan et al., 2017). As these actions extend from single cells to distributed circuits, the causal, mediating or moderating roles of sex steroids are evident across several psychiatric conditions (Crowley, 2017; McHenry et al., 2014; Morrell et al., 2005; Pinares-Garcia et al., 2018).

Sex steroids organise hypothalamic circuits during sensitive periods in the perinatal and adolescent stages, shaping them into male- or female-typical patterns through processes of masculinisation, defeminisation and feminisation. This shapes the adult brain's responsiveness to hormones (Lemaire et al., 2013; Lenz & McCarthy, 2010; McCarthy, 2008). In adulthood, these enduring organisational effects are complemented by the activational, plastic and reversible actions of gonadal steroids on hypothalamic activity. This activity is central for sexual motivation, cognition and behaviour (Campbell & Herbison, 2014). Neuroimaging studies in transgender individuals show that testosterone therapy versus oestradiol and anti-androgen therapy induces opposite changes in hypothalamic volume and mean diffusivity. This links sex steroids to sexual arousal and highlights the importance of hypothalamus-hormone associations are crucial for understanding the effects of gender-affirming hormone therapy (Kranz et al., 2018; Pol et al., 2006).

Recognising that the adult brain remains responsive to sex steroids clarifies why substantial exogenous exposures can still induce measurable neural and functional alterations later in life, as demonstrated by gender-affirming hormone therapy. Investigating the effects of GAHT on the brains of transgender individuals using neuroimaging offers a unique opportunity to

examine the impact of of GAHT and thus sex hormones on brain structure and function in vivo (Gooren et al., 2008; Kranz et al., 2018).

Sexual Desire

Sexual desire, sexual activity, and sexual satisfaction are widely recognised as central to human life. Sexual desire is defined as a motivational state shaped by various factors throughout an individual's lifespan (Levine, 2002, 2003). These factors include biological drives, cognitive-affective processes, relational context, and sociocultural learning (Carvalho & Nobre, 2010). Rather than being a unitary construct, sexual desire comprises processes that fluctuate according to internal states, such as fantasies and moods, and external triggers, such as signals from a partner, sensory cues, and situational affordances and constraints (Carvalho & Nobre, 2010; Hayes et al., 2008; Levine, 2002, 2003). In line with this view, sexual desire can be specified as interest in sexual activity indexed by the amount and strength of thoughts directed toward sexual stimuli (Spector et al., 1996). Sexual desire is therefore described as the sum of forces inclining a person towards or away from sexual behaviour, emphasising that everyone experiences it episodically and variably (Levine, 2002). A common distinction separates dyadic desire, which is oriented towards intimacy and shared sexual activity, and solitary desire, which is oriented towards self-stimulated sexual behaviour (Spector et al., 1996). The Sexual Desire Inventory (SDI) is a widely used self-report instrument that captures this distinction (Spector et al., 1996). The SDI consists of 14 items that assess interest in sexual activity, which is conceptualised as the frequency and intensity of desire-related thoughts and feelings. It obtains two subscale scores: dyadic sexual desire (items 1-9), reflecting desire for sexual activity and intimacy with another person, and solitary sexual desire (item 10-13), reflecting interest in sexual behaviour alone. A total sexual desire score can be calculated by summing the two subscales (range 0-101), with higher scores indicating a higher level of desire (Spector et al., 1996). Most items are rated on an 8-point Likert-type scale measuring the frequency or intensity of desire. Items 1, 2 and 10, however refer to the previous month and use a 7-point scale. Item 14 assesses how long an individual can feel comfortable without any sexual activity and is rated on a 9-point scale before being recoded. In previous psychometric evaluations, Cronbach's alpha values of approximately $\alpha = .93$ for dyadic desire and $\alpha = .91$ for solitary desire have been reported (Dosch et al., 2016), supporting the SDI as a reliable measure that differentiates partnered and solitary aspects of sexual desire. This conceptualisation and its operationalisation in the SDI allow individual differences and changes in sexual desire to be examined in relation to biological and psychosocial influences.

Within this motivational landscape, endocrine factors are important, though not exclusive, contributors. Reviews of testosterone replacement in hypogonadal cisgender men report improvements in sexual desire (Bancroft, 2005), whereas supplementation has little effect in eugonadal men (Basar et al., 2005; Gades et al., 2008). This pattern points to a threshold effect in which androgens support sexual desire up to a sufficiency point, while variation within the physiological range is a poor driver of differences in sexual desire (Bancroft, 2005; Wierckx, Elaut, et al., 2014). As testosterone is aromatised to oestradiol in many tissues, oestradiol has been suggested as a mediator of certain androgen effects on desire. However, correlations between circulating oestradiol and sexual desire are generally weak or absent in cisgender men (Basar et al., 2005; Gades et al., 2008). In cisgender women, ovarian steroids modulate sexual desire across reproductive stages and menstrual cycles (Cappelletti & Wallen, 2016). However, debate persists regarding the respective roles of oestradiol and testosterone. In daily sampling designs, oestradiol shows small prospective positive associations with sexual desire over short time intervals, whereas progesterone reliably predicts lower sexual desire on the same day and at one- to two day lags, and endogenous testosterone is not a consistent predictor at any time scale (Roney & Simmons, 2013). During the menopausal transition, a decline in oestradiol is associated with a reduction in self-reported desire and sexual responsiveness (Cappelletti & Wallen, 2016; Dennerstein et al., 2002). In contrast, testosterone levels are not consistently related to desire or activity (Cappelletti & Wallen, 2016). This pattern is consistent with studies showing that oestrogen-only regimens which achieve periovulatory oestradiol levels can increase desire in postmenopausal women (Cappelletti & Wallen, 2016; Dow et al., 1983). Supraphysiological testosterone may augment the effects of low-dose oestrogen, but physiological testosterone alone appears insufficient and the underlying mechanisms remain unclear (Bolour & Braunstein, 2005; Cappelletti & Wallen, 2016). Taken together, these studies indicate that ovarian steroids modulate the intensity and timing of sexual desire rather than initiating it. Oestradiol appears to act both centrally and peripherally, whereas progesterone functions predominanty as an inhibitory signal.

Gender-affirming hormone therapy introduces an additional element by altering both the sex steroid milieu and the psychosocial context in which sexual motivation is experienced. Short-term follow-ups consistently demonstrate that virilising therapy increases desire in TM, while feminising therapy involving oestrogen and antiandrogens reduces desire in TW (Defreyne et al., 2020; Van Dijk et al., 2019; Wierckx, Elaut, et al., 2014; Wierckx et al., 2011). The most significant changes are typically evident within three months (Defreyne et al., 2020; Van Dijk

et al., 2019). Shorter exposure to testosterone has been associated with more symptoms of high desire early in treatment (Wierckx, Van Caenegem, et al., 2014).

However, over longer periods, the pattern becomes more complex: desire in TW tends to return to or exceed baseline levels, while group means in TM converge towards pre-treatment levels. This suggests that sex steroids are not the sole determinants of sustained sexual motivation (Defreyne et al., 2020; Van Dijk et al., 2019).

In addition to sex steroids, psychological processes co-determine the expression and variability of sexual desire (Carvalho & Nobre, 2010). Cognitive schemas about sexuality, attentional focus and emotional regulation influence whether erotic cues are noticed and evaluated as appealing, and whether they are permitted to influence behaviour. In women, cognitive distraction during sexual activity and negative automatic thoughts have been linked to lower desire. Meanwhile, relationship quality and broader motivational states have been found to contribute to dyadic desire beyond individual trait levels (Carvalho & Nobre, 2010, 2011). Operating alongside endocrine influences, mood and psychopathology co-determine sexual desire, with depressive and anxiety symptoms constantly associated with diminished sexual interest. However, some studies suggest an alternative pattern, whereby solitary desire increases while dyadic desire decreases (Dennerstein et al., 2002; Frohlich & Meston, 2002). This points to the existence of distinct motivational systems for partnered and solitary sexuality (Bodenmann et al., 2010; Dennerstein et al., 2002; Dosch et al., 2016; Frohlich & Meston, 2002). Even in tightly sampled endocrine studies, the external context exerts a detectable effect. For example, weekend timing has been shown to predict higher desire, independent of concurrent hormone concentrations. This illustrates how social structure can increase or reduce biological signals (Roney & Simmons, 2013). For transgender individuals, experiencing GI is a key psychological factor that drives sexual desire. Improvements in dysphoria, body comfort and stigma-related stress after transition are likely to account for some of the change in sexual desire (Wierckx, Van Caenegem, et al., 2014).

At a neural level, the endocrine and psychological influences on sexual desire converge in brain regions that integrate motivational and hormonal signals, most notably the hypothalamus. Converging neuroimaging evidence points to a sexual desire network that includes hypothalamic regions together with the ventral striatum, midbrain dopaminergic areas, amygdala, insula and anterior cingulate cortex (Cacioppo, 2017; Cacioppo et al., 2012). This network is reliably engaged when individuals see erotic stimuli and report sexual desire, indicating that hypothalamic nuclei operate in concert with limbic and reward-related regions to support the motivational and autonomic components of sexual desire (Cacioppo, 2017;

Cacioppo et al., 2012). In women with hypoactive sexual desire disorder, parts of this network, including hypothalamic and limbic regions, show reduced activation during erotic stimulation, consistent with attenuated recruitment of neural systems that normally support sexual desire (Cacioppo, 2017). Findings from animal models complement these human data by demonstrating that the medial preoptic area and the anterior hypothalamus are essential for male-typical sexual behaviour, acting as sites where sex steroids are integrated with mesolimbic dopamine pathways (Micevych & Meisel, 2017; Paredes, 2003; Pfaus, 2009). Taken together, this translational evidence indicates that the hypothalamic nuclei are part of neural circuits linking bodily and hormonal states to reward-related processing. They also appear to play a role in the development of sexual motivation and behaviour. However, the precise mechanisms involved in humans remain unclear.

Therefore, a biopsychosocial perspective remains essential as a primary framework for understanding how desire is generated, inhibited and reconfigured over time.

Gender-affirming hormone therapy

GAHT is a process in which oestradiol, progesterone, or testosterone, among some other components, are administrated to induce secondary sex characteristics that align with the gender identity of person receiving treatment. This is tailored to their individual transition goals, while taking into account medical comorbidities and the risks associated with hormone use (Hembree et al., 2017; Kranz et al., 2020; Unger, 2016). TM who seek GAHT are given testosterone, which induces masculinisation and suppresses endogenous oestrogen and associated feminising features, while TW are given oestradiol and, when oestradiol alone does not sufficiently reduce testosterone, an antiandrogen is added. It is equally important to note that not all transgender individuals pursue hormonal intervention as part of their transition (D'hoore & T'Sjoen, 2022; Hembree et al., 2017; Unger, 2016). Both the World Professional Association for Transgender Health (WPATH) and the Endocrine Society have created transgender-specific guidelines to serve as a framework for healthcare providers caring for gender minority patients (Hembree et al., 2017; T'Sjoen et al., 2020). The WAPTH suggests that adults seeking hormone therapy should have persistent and well-documented gender incongruence; the capacity to make informed decisions and provide consent, have reached the age of majority, and have reasonably controlled mental health concerns. The Endocrine Society guideline together with the European Society for Sexual Medicine position statement, provides protocols with specific information on hormone types and suggested dosing to support personalised care (Coleman et al., 2012; Hembree et al., 2017; T'Sjoen et al., 2020). Somatic changes usually begin within months and

accrue over about two years, though there is substantial individual variability. TM typically experience growth of facial and body hair, acne, deepening of the voice, a reduction in body fat and an increase in lean mass. They also experience cessation of menstruation (amenorrhea), vaginal atrophy, and clitoral enlargement. TW show breast development, redistribution of body fat, softer and less oily skin, a reduction in testicular volume, and decreased male-pattern hair growth (Unger, 2016). As outlined in the Sexual Desire section, sexual desire increases in TM and declines in TW. Rising libido in TM is often evident early on after the start of testosterone , while lower androgen levels in TW are associated with decreased sexual desire (Wierckx, Elaut, et al., 2014). In both groups, GAHT has been associated with improvements in quality of life, which are observed alongside shifts in body contours towards the affirmed gender linked to reductions in body uneasiness (Fisher et al., 2016; Gorin-Lazard et al., 2012). Consistent with these observations, a recent review further reports that most studies have found reductions in GD and body dissatisfaction, alongside improvements in psychological well-being and quality of life (Van Leerdam et al., 2023).

Aim of the study

The overall aim of the study was to evaluate changes in sexual desire and hypothalamic volume after approximately four months of high-dose gender-affirming hormone therapy (GAHT) in TM and TW. More specifically, the primary aim was to examine whether changes in testosterone and oestradiol following the initiation of GAHT are associated with changes in dyadic and solitary sexual desire. The secondary aim was to investigate whether changes in hypothalamic volume moderate these associations between changes in sex steroid levels and changes in sexual desire.

Hypotheses

Based on these aims, the following hypotheses were formulated.

Transgender Men – Primary Hypotheses

$H0_{1a}$: In transgender men, changes in testosterone and oestradiol levels following GAHT are not associated with changes in dyadic or solitary sexual desire (SDI 1 and SDI 2).

H1a: In transgender men, a concurrent increase in testosterone levels and decrease in oestradiol levels following gender-affirming hormone therapy is associated with an increase in dyadic sexual desire (SDI 1).

H1b: In transgender men, a concurrent increase in testosterone levels and decrease in oestradiol levels following gender-affirming hormone therapy is associated with an increase in solitary sexual desire (SDI 2).

Transgender Men – Secondary Hypotheses

$H0_2$: In transgender men, changes in hypothalamic volume do not moderate the associations between changes in testosterone or oestradiol levels and changes in dyadic or solitary sexual desire.

H2a: In transgender men, the relationship between a concurrent increase in testosterone levels and decrease in oestradiol levels and dyadic sexual desire is moderated by changes in hypothalamic volume.

H2b: In transgender men, the relationship between a concurrent increase in testosterone levels and decrease in oestradiol levels and solitary sexual desire is moderated by changes in hypothalamic volume.

Transgender Women – Primary Hypotheses

$H0_{1b}$: In transgender women, changes in testosterone and oestradiol levels following GAHT are not associated with changes in dyadic or solitary sexual desire (SDI-1 and SDI-2).

H1c: In transgender women, a concurrent decrease in testosterone levels and increase in oestradiol levels following gender-affirming hormone therapy is associated with a decrease in dyadic sexual desire (SDI 1).

H1d: In transgender women, a concurrent decrease in testosterone levels and increase in oestradiol levels following gender-affirming hormone therapy is associated with a decrease in solitary sexual desire (SDI 2).

Transgender Women – Secondary Hypotheses

$H0_{2b}$: In transgender women, changes in hypothalamic volume do not moderate the associations between changes in testosterone or oestradiol levels and changes in dyadic or solitary sexual desire.

H2c: In transgender women, the relationship between a concurrent decrease in testosterone levels and increase in oestradiol levels and dyadic sexual desire is moderated by changes in hypothalamic volume.

H2d: In transgender women, the relationship between a concurrent decrease in testosterone levels and increase in oestradiol levels and solitary sexual desire is moderated by changes in hypothalamic volume.

Methods and Materials

Study design

The present study is part of the already approved longitudinal single-centre trial (EK 1104/2015) at the Medical University of Vienna, which was conducted in a single-blind, controlled, observational design. All procedures complied with the Declaration of Helsinki and the Good Scientific and Clinical Practice guidelines (GCP) of the Medical University of Vienna, and all participants gave written informed consent. TM and TW, as well as age-matched cisgender women and cisgender men, underwent two MRI sessions (M1 and M2), with an interval of approximately 145 days between them. For transgender participants M1 took place before the initiation of gender-affirming hormone therapy, while M2 took place after at least 12 weeks of continuous treatment. Cisgender controls underwent two scans with a comparable time interval but did not receive hormonal treatment. At both times, participants received a structural MRI scan, completed the Sexual Desire Inventory (SDI) and provided blood samples to assess plasma testosterone and oestradiol levels. Gender-affirming hormone therapy was initiated immediately after M1 for transgender participants, following individualised high-dose regimens according to the standard protocols of the Department of Obstetrics and Gynaecology at the Medical University of Vienna. The present thesis focuses on the transgender subsample and analyses hypothalamic volume, sex steroid levels, and SDI scores obtained at M1 and M2.
D

Study Population

This study included a total of 29 transgender individuals, comprising 10 TW and 19 TM participants. All participants were recruited at the Gender Identity Disorder Unit of the Department of Gynaecology and Obstetrics, at the General Hospital Vienna, which is the leading facility in Austria for individuals seeking gender-affirming hormone treatment.

All transgender participants fulfilled the diagnostic criteria for GD according to the DSM-5. These criteria were established by experienced clinicians based on psychological and psychiatric assessments, as well as clinical interviews conducted by trained psychiatrists. To be eligible, participants were required to be at least 18 years of age and able to provide written informed consent. They also had to be in good general physical and mental health. General health status was assessed by medical history, physical examination, laboratory screening, electrocardiogram and a structured clinical interview (Structured Clinical Interview for DSM-IV Axis I Disorders, Clinical Version; First et al., 2016). A detailed overview of the inclusion and exclusion criteria for transgender participants is provided in Table 2.

Table 2: In- and Exclusion Criteria for transgender individuals.

Inclusion Criteria	Exclusion Criteria
- DSM-5 diagnosis of Gender Dysphoria (DSM-5: 302.85; ICD-10: F64.1) - Somatic health based on history, physical examination, electrocardiogram, laboratory screening, SCID - Willingness and competence to sign the informed consent form	- Concomitant major medical or neurological illness - Internal or neurologic medical histories as well as pregnancy or breastfeeding - Other DSM-5 Axis-I comorbidities, determined by a structural clinical interview (SCID), especially body dysmorphic disorder (DSM-5: 300.7; ICD-10: F45.22), schizophrenia spectrum and other psychotic disorders - steroid hormone treatment within 6 months prior to inclusion - treatment with psychotropic agents such as Selective Serotonin Reuptake Inhibitors (SSRIs) - any contraindication for MRI - clinically relevant abnormal values in routine laboratory screening or general physical examination

- current substance abuse or current or past substance related disorder
- failure to comply with the study protocol or to follow the instructions of the investigating team

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Instruments

The following section provides an overview of the instruments and measurement procedures used in this study, including MRI acquisition and processing, assessment of sexual desire, and hormone analysis.

MRI Acquisition and Processing

All MRI data were acquired using a 3 Tesla Siemens Magnetom Prisma scanner equipped with a 64-channel head coil at the High-Field MR Centre of the Medical University of Vienna. High-resolution whole-brain T1-weighted images were obtained at both measurement points (M1 and M2) using the following parameters: TE / TR =2.91 / 2000 ms; inversion time =900 ms; flip angle =9 °; matrix =240×256, 176 slices; voxel size =1.0 mm^3; acquisition time =7:59 min. During scanning, participants were instructed to remain still, keep their eyes open and stay awake, in order to minimise motion artefacts. The full MRI session lasted approximately 60 minutes, with structural imaging accounting for around 20 minutes.

The structural data were processed using the FreeSurfer software suite (version 7.2), with the standard cross-sectional pipeline applied first, followed by the longitudinal stream to improve within-subject reliability. The hypothalamus and its subunits were segmented using the automated hypothalamic segmentation tool distributed with FreeSurfer, which assigns voxels to five anatomically defined subunits per hemisphere (anterior inferior, anterior superior, posterior, tubular inferior, tubular superior). In addition, volumetric estimates were obtained for the left and right whole hypothalamus (Bocchetta et al., 2015; Makris et al., 2013). Exemplary segmentations of the hypothalamic subunits are shown in Figure 1.

The segmentations were visually inspected by trained neuroscientist and datasets of insufficient quality were excluded.

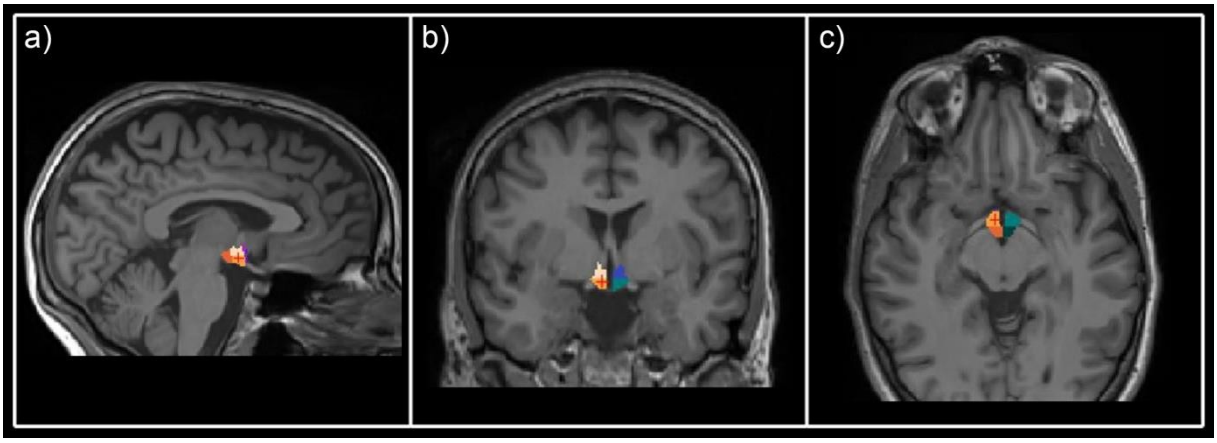

Figure 1: Exemplary masks for the hypothalamus subunits in (a) sagittal, (b) coronal and (c) horizontal view.

Sexual Desire Inventory

Sexual desire was assessed at both time points using the SDI (Spector et al., 1996). A detailed conceptual description of the instrument can be found in Chapter 2.6. For the present study, dyadic and solitary SDI subscale scores were calculated according to the original scoring guidelines, and participants completed the questionnaire at both M1 and M2.

Medication

The GHT protocol was implemented at the Department of Obstetrics & Gynecology, Division of Gynecologic Endocrinology and Reproductive Medicine, Medical University of Vienna, Austria.

Treatment options for TM:

- either 1000 mg testosterone undecanoate every 8–16 weeks (Nebido 1000 mg/4 ml i.m.) or up to 50 mg testosterone per day (Testogel 50 mg/day or Testavan 23 mg/pump, 1–2 pumps/day, or testosterone cream as magistral formulation, 12.5 mg/pump, 3–4 pumps/day, administered transdermally)
- if menstruation persisted, TM were additionally prescribed either lynestrenol (Orgametril 5 mg, 2–3 tablets/day, p.o.) or desogestrel (Moniq Gynial or Cerazette 0.075 mg/day, p.o.)

Treatment options for TW:

- daily cyproterone acetate (Androcur 50 mg/day) in combination with either transdermal estradiol (Estramon 100 µg transdermal patch, 2×/week, or Estrogel gel 0.75–1.5 mg/day, transdermally) or oral estradiol (Estrofem 4 mg/day, p.o.)
- in cases of pronounced hair loss, an alpha-5-reductase inhibitor (Finasterid 2.5 mg/48 h, Actavis/Arcana/Aurobindo, p.o.) were described
- selected participants received GnRH analogues such as triptorelin (decapeptyl 0.1 mg/day, subcutaneously)

Hormone Assessment

Venous blood samples were collected at both time points before the MRI session to quantify circulating sex steroid levels. Plasma concentrations of testosterone and oestradiol were analysed using standard clinical laboratory procedures at the Medical University of Vienna. These endocrine measures were used to characterise the hormonal changes associated with the initiation of gender-affirming hormone therapy and were subsequently examined in relation to hypothalamic volume and sexual desire.

Statistical Analysis

All statistical analyses were conducted using IBM SPSS Statistics (version 25). Descriptive statistics are reported as means and standard deviations. Model assumptions and residuals were inspected visually to check for normality and homoscedasticity. All tests were two-tailed, and the level of statistical significance was set at α =.0.5.

To examine the effects of gender-affirming hormone therapy on sexual desire, linear-mixed models (LMMs) were estimated using the MIXED procedure with restricted maximum likelihood (REML). The analyses were conducted separately for TM and TW. In each model, the SDI scores served as the dependent variable. The subject identifier (ID) was specified as the subject variable, and measurement (M1 versus M2) was modelled as a within-subject repeated factor and included as a fixed effect to test for changes in SDI scores over time.

In addition to the fixed effects of measurement, age, sex hormone level (testosterone or oestradiol), and the hypothalamic region of interest (ROI) volume were included as continuous covariates. Dyadic and solitary SDI subscale score were analysed in separate LMMs using the same model structure. For the hypothalamic predictor, separate models were run for each of the

12 ROIs described above, with the corresponding ROI volume entered as a covariate in each model.

Furthermore, a combined interaction term (measurement x group x age x hormone level x hypothalamic ROI volume) was specified as an omnibus interaction. This higher-order interaction was included to test whether the association between sex hormone levels and sexual desire depended jointly on time, age and hypothalamic volume, that is, whether hypothalamic volume moderated hormone-desire associations in a time- and group dependent manner.

For the repeated measurement factor, a covariance structure allowing for correlated residuals between M1 and M2 was specified to account for within-subject dependence, and, where alternative covariance structures were compared, the structure with the lowest Akaike Information Criterion (AIC) was selected.

Results

Descriptive Statistics

A total of 29 transgender individuals were included in the substudy, comprising 19 TM and 10 TW. At study completion, TM had a mean age of 25.2 years (SD = 7.4, range 18-46), whereas TW had a mean age of 28.3 years (SD = 9.0, range 19-52). Mean oestradiol and testosterone levels (M ± SD) for each group and time point are shown in Table 3. Table 4 presents the mean dyadic and solitary SDI scores (M ± SD) for each group and time point. The distribution of the SDI scores by group and time point is illustrated in Figures 4 – 7. Figure 2 and 3 show the distributions of the testosterone levels in TM and oestradiol levels in TW before and after GAHT.

Table 3: Mean hormone levels (± SD) for each group and time point.

	Transgender Men		Transgender Women	
	M1	M2	M1	M2
oestradiol (pg/ml)	99.6 ± 92.6	31.8 ± 21.3	21.2 ± 10.6	34.8 ± 19.9
testosterone (ng/ml)	0.1 ± 0.1	2.1± 1.3	2.6 ± 0.7	0.1 ± 0.1

Table 4 Mean SDI scores (± SD) for each group and time point.

	Transgender Men		Transgender Women	
	M1	M2	M1	M2
dyadic SD (SDI 1)	17.4 ± 9	22.9 ± 8.3	20.3 ± 5.7	19.1 ± 7.6
solitary SD (SDI 2)	12.9 ± 8.3	20.9 ± 9.5	16 ± 9.3	13.4 ± 9.4

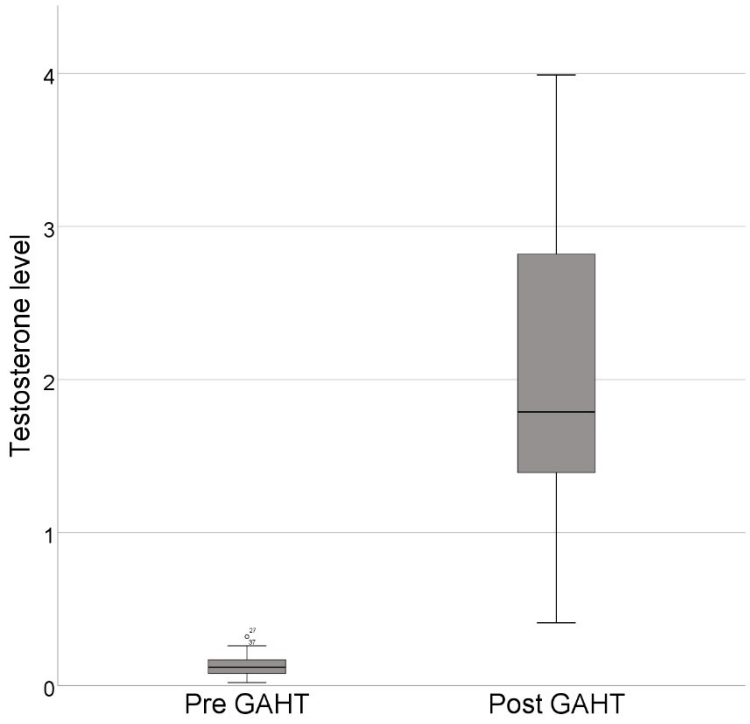

Figure 2: Testosterone levels in transgender men before and after gender-affirming hormone therapy (GAHT).

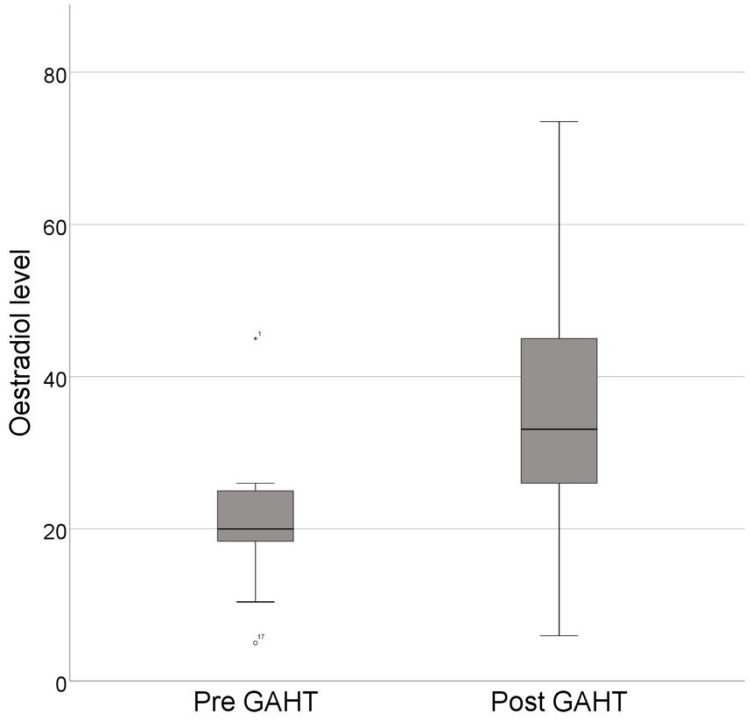

Figure 3: Oestradiol levels in transgender women before and after gender-affirming hormone therapy (GAHT).

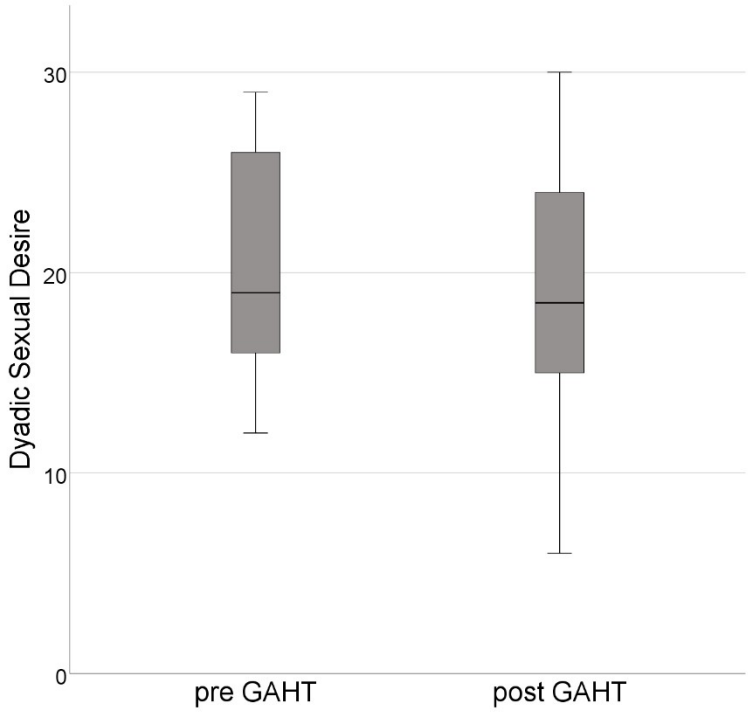

Figure 4: Dyadic sexual desire scores (SDI 1) in transgender women before and after gender-affirming hormone therapy (GAHT).

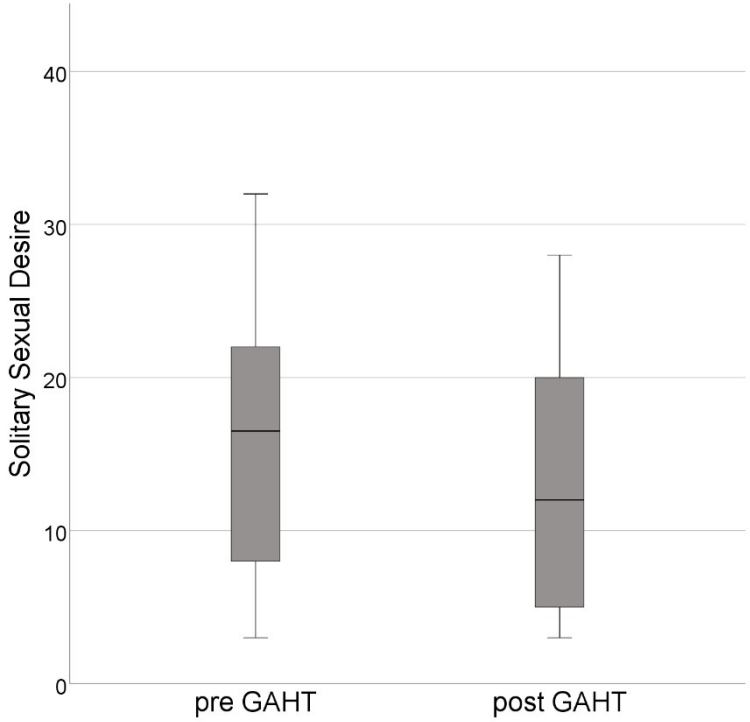

Figure 5: Solitary sexual desire (SDI 2) scores in transgender women before and after gender-affirming hormone therapy (GAHT).

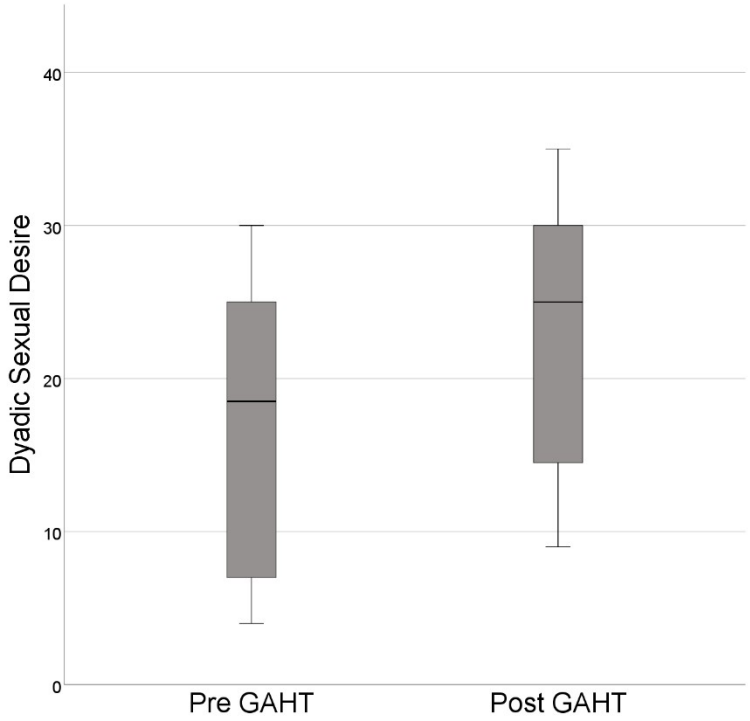

Figure 6: Dyadic sexual desire scores (SDI 1) in transgender men before and after gender-affirming hormone therapy (GAHT).

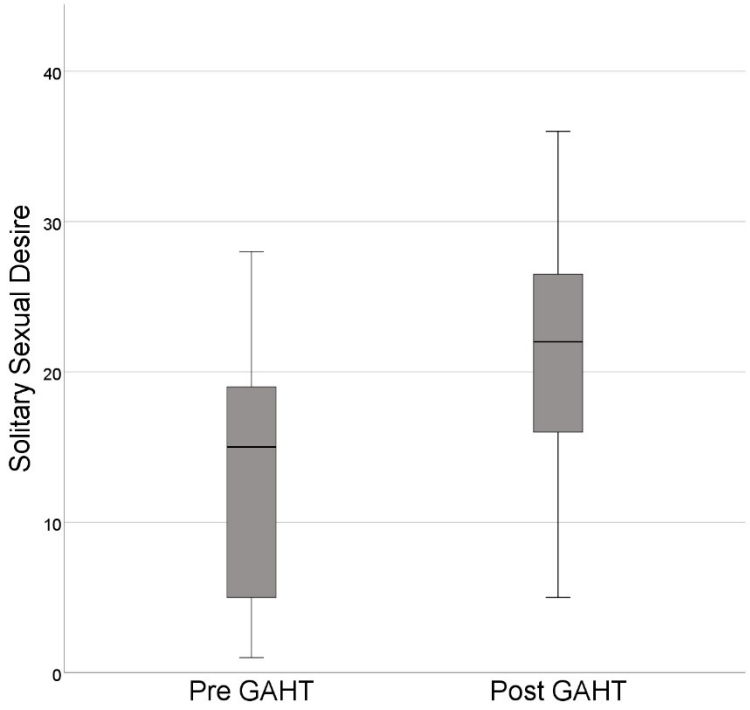

Figure 7: Solitary sexual desire scores (SDI 2) in transgender men before and after gender-affirming hormone therapy (GAHT).

Associations between sex hormone levels and sexual desire

In the present study, TM underwent masculinising GAHT with testosterone, whereas TW received feminising oestradiol-based regimens. As shown in Table 4, this resulted in marked increases in testosterone levels and decreases in oestradiol levels in TM across the two measurement time points, while TW showed pronounced reductions in testosterone levels and increases in oestradiol.

Dyadic Sexual Desire (SDI 1)

Against this background, dyadic sexual desire (SDI 1) was examined in relation to changes in testosterone and oestradiol levels, analysed separately for TW and TM. Linear mixed models were fitted for SDI 1, with SDI 1 scores as the dependent variable and the three-way interaction between measurement, age, and sex hormone level as the predictor of interest (see Table 5). In TW, the interaction term involving oestradiol was significant ($F = 40.88$, $p < .001$), with larger increases in oestradiol being associated with more pronounced decreases in dyadic sexual desire, whereas the interaction involving testosterone was not significant ($F = 0.34$, $p = .723$). In TM, the three-way interaction with testosterone reached significance ($F = 4.93$, $p = .020$), with higher testosterone levels over time being associated with higher dyadic sexual desire

scores, while the interaction including oestradiol did not reach significance (F = 0.20, *p* = *.824*). The F- and p-values for these models are shown in Table 5.

Table 5: Effects of sex hormone levels on dyadic sexual desire (SDI 1) in transgender men and transgender women.

Group	Hormone	*F-value*	*p-value*
Transgender Women	testosterone	0.34	.723
Transgender Women	oestradiol	40.88	< .001
Transgender Men	testosterone	4.93	.02
Transgender Men	oestradiol	0.20	.824

Note. SDI-1 = dyadic sexual desire. Values refer to the three-way interaction time × age × hormone from linear mixed models. F-values are rounded to two decimal places; p-values to three decimals (p < .001 for values smaller than .001).

Solitary Sexual Desire (SDI 2)

Solitary sexual desire (SDI 2) was examined in relation to changes in testosterone and oestradiol separately for TW and TM. In TW, the interaction term involving oestradiol was significant (F = 21.98, *p* = *.001*), with larger increases in oestradiol being associated with more pronounced decreases in SDI 2 scores, whereas the interaction involving testosterone did not reach significance (F = 4.14, *p* = *.067*). In TM, the three-way interaction with testosterone was significant (F = 4.65, *p* = *.024*), with higher testosterone levels over time being associated with higher SDI 2 scores, while the interaction including oestradiol, was not (F = 2.87, *p* = *.084*). For SDI 2, the relevant F- and p-values for the time x age x hormone interaction are summarised in Table 6.

Table 6: Effects of sex hormone levels on solitary sexual desire (SDI 2) in transgender men and transgender women.

Group	Hormone	*F-value*	*p-value*
Transgender Women	testosterone	4.14	.067
Transgender Women	oestradiol	21.98	.001
Transgender Men	testosterone	4.65	.024
Transgender Men	oestradiol	2.87	.084

Note. SDI-2 = solitary sexual desire. Values refer to the three-way interaction time × age × hormone from linear mixed models.

Associations between sex hormone levels, hypothalamic volume, and sexual desire

In TW, results for dyadic sexual desire (SDI 1) across the 12 hypothalamic regions of interest are summarised in Table 7. In TW and TM, dyadic and solitary sexual desire was examined in relation to sex hormone levels and hypothalamic volume across the predefined regions of interest. Separate linear mixed models were estimated for each of the 12 hypothalamic ROIs. In these models, the higher-order interaction between measurement, age, sex hormone level and hypothalamic ROI volume was used as the predictor of interest.

Dyadic sexual desire (SDI 1) in Transgender Women

For testosterone, none of the interaction terms reached the predefined threshold for statistical significance in any of the hypothalamic regions.

In addition, analyses with oestradiol as the hormone predictor yielded statistically significant interactions terms for all hypothalamic ROIs. For the left and right whole hypothalamus, the interaction effects were F = 21.27, $p = .002$ and F = 43.06, $p < .001$, respectively. Significant interactions effects were also observed for all anterior, posterior and tubular subunits in both hemispheres. All corresponding F- and p-values are presented in Table 7.

Table 7: Effects of sex hormone levels and hypothalamic ROI volume on dyadic sexual desire (SDI 1) in transgender women.

Group	Hormone	ROI	*F-value*	*p-value*
Transgender Women	testosterone	whole left	0.30	.75
Transgender Women	testosterone	whole right	0.36	.71
Transgender Women	testosterone	left anterior inferior	0.06	.94
Transgender Women	testosterone	left anterior superior	0.81	.49
Transgender Women	testosterone	left posterior	0.21	.82
Transgender Women	testosterone	left tubular inferior	0.88	.45
Transgender Women	testosterone	left tubular superior	0.46	.65
Transgender Women	testosterone	right anterior inferior	0.47	.65
Transgender Women	testosterone	right anterior superior	0.70	.53

Transgender Women	testosterone	right posterior	1.04	.43
Transgender Women	testosterone	right tubular inferior	0.53	.62
Transgender Women	testosterone	right tubular superior	0.26	.78
Transgender Women	oestradiol	whole left	21.27	.002
Transgender Women	oestradiol	whole right	43.064	<.001
Transgender Women	oestradiol	left anterior inferior	6.23	.019
Transgender Women	oestradiol	left anterior superior	42.42	.003
Transgender Women	oestradiol	left posterior	35.40	< .001
Transgender Women	oestradiol	left tubular inferior	22.69	.001
Transgender Women	oestradiol	left tubular superior	11.87	.008
Transgender Women	oestradiol	right anterior inferior	471.21	< .001
Transgender Women	oestradiol	right anterior superior	12.12	.006
Transgender Women	oestradiol	right posterior	7.10	.018
Transgender Women	oestradiol	right tubular inferior	17.92	.002
Transgender Women	oestradiol	right tubular superior	23.35	.002

Note. SDI-1 = dyadic sexual desire; ROI = region of interest. Values represent F- and p-values for the interaction measurement × age × hormone × hypothalamic ROI volume from linear mixed models.

Solitary sexual desire (SDI 2) in Transgender Women

In TW, the results for solitary sexual desire (SDI 2) across the 12 hypothalamic regions of interest are summarised in Table 8. For testosterone, the interaction term between measurement, age, testosterone level and hypothalamic ROI volume was not statistically significant for the whole hypothalamus (whole left: F = 2.91, $p = .12$; whole right: F = 3.26, $p = .109$), whereas the left tubular superior subunit showed a significant interaction (F = 4.80, $p = .046$).

In contrast, analyses with oestradiol as the hormone predictor showed statistically significant interaction terms for almost all hypothalamic ROIs. For the left and right whole hypothalamus,

the interaction effects were F = 33.29, *p = .001* and F = 33.64, *p < .001*, respectively. Significant interactions were also observed for the left anterior inferior (F = 17.77, *p =.006*), left anterior superior (F = 29.00, *p =.001*), left posterior (F = 9.26, *p =.008*), left tubular inferior (F = 31.66, *p <.001*) and left tubular superior (F = 7.50, *p =.019)* subunits. In the right hemisphere, significant interaction effects were found for the anterior inferior (F = 14.98, *p <.001*), anterior superior (F = 18.49, *p =.002*), tubular inferior (F = 93.01, *p <.001*) and tubular superior (F= 30.51, *p =.001*) regions, whereas the right posterior subunit did not reach statistical significance (F = 3.14, *p =.085*).

Table 8: Effects of sex hormone levels and hypothalamic ROI volume on solitary sexual desire (SDI 2) in transgender women.

Group	Hormone	ROI	*F-value*	*p-value*
Transgender Women	testosterone	whole left	2.91	.12
Transgender Women	testosterone	whole right	3.26	.109
Transgender Women	testosterone	left anterior inferior	1.29	.327
Transgender Women	testosterone	left anterior superior	3.47	.096
Transgender Women	testosterone	left posterior	1.77	.232
Transgender Women	testosterone	left tubular inferior	2.7	.132
Transgender Women	testosterone	left tubular superior	4.80	.046
Transgender Women	testosterone	right anterior inferior	3.32	.104
Transgender Women	testosterone	right anterior superior	3.47	.088
Transgender Women	testosterone	right posterior	4.49	.077
Transgender Women	testosterone	right tubular inferior	3.31	.104
Transgender Women	testosterone	right tubular superior	2.86	.144
Transgender Women	oestradiol	whole left	33.29	.001
Transgender Women	oestradiol	whole right	33.64	< .001

Transgender Women	oestradiol	left anterior inferior	17.77	.006
Transgender Women	oestradiol	left anterior superior	29.004	.001
Transgender Women	oestradiol	left posterior	9.26	.008
Transgender Women	oestradiol	left tubular inferior	31.66	< .001
Transgender Women	oestradiol	left tubular superior	7.50	.019
Transgender Women	oestradiol	right anterior inferior	14.98	< .001
Transgender Women	oestradiol	right anterior superior	18.49	.002
Transgender Women	oestradiol	right posterior	3.14	.085
Transgender Women	oestradiol	right tubular inferior	93.01	< .001
Transgender Women	oestradiol	right tubular superior	30.51	.001

Note. SDI 2 = solitary sexual desire; ROI = regions of interest. Values represent F- and p-values for the interaction measurement x age x hormone x hypothalamic ROI volume from liner mixed models.

Dyadic sexual desire (SDI 1) in Transgender Men

In TM, results for dyadic sexual desire across 12 hypothalamic regions of interest are summarised in Table 9. For Testosterone, the interaction between measurement, age, testosterone level and hypothalamic ROI volume was statistically significant for both the left and right whole hypothalamus (whole left: F = 4.72, *p =.024*; whole right: F = 4.88, *p =0.22*). Significant interaction effects were also observed for several subunits, including the left anterior superior (F = 5.83, *p =.012*), left tubular inferior (F = 4.59, *p =.027*), left tubular superior (F = 5.99, *p =.012*), right tubular inferior (F = 4.79, *p =.022*) and right tubular superior (F = 6.67, *p =.008*).

For oestradiol, interaction terms were not statistically significant for the whole hypothalamus (whole left: F = 0.64, *p =.112*; whole right: F = 0.58, *p =.114*) and for most hypothalamic subunits (e.g., left anterior inferior: F = 0.97, *p =.209*; left posterior: F = 0.94, *p =.592*; right anterior inferior: F = 0.94, *p =.293*; right tubular superior: F = 0.50, *p =.080*). Significant interaction effects were observed for the left anterior superior (F = 0.50, *p =.007*) and left tubular superior (F = 0.34, *p =.027*) subunits.

Table 9: Effects of sex hormone levels and hypothalamic ROI volume on dyadic sexual desire (SDI 1) in transgender men.

Group	Hormone	ROI	*F-value*	*p-value*
Transgender Men	testosterone	whole left	4.72	.024
Transgender Men	testosterone	whole right	4.88	.022
Transgender Men	testosterone	left anterior inferior	1.74	.209
Transgender Men	testosterone	left anterior superior	5.83	.012
Transgender Men	testosterone	left posterior	2.85	.086
Transgender Men	testosterone	left tubular inferior	4.59	.027
Transgender Men	testosterone	left tubular superior	5.99	.012
Transgender Men	testosterone	right anterior inferior	3.23	.064
Transgender Men	testosterone	right anterior superior	2.85	.086
Transgender Men	testosterone	right posterior	2.90	.083
Transgender Men	testosterone	right tubular inferior	4.79	.022
Transgender Men	testosterone	right tubular superior	6.67	.008
Transgender Men	oestradiol	whole left	0.64	.112
Transgender Men	oestradiol	whole right	0.58	.114
Transgender Men	oestradiol	left anterior inferior	0.97	.209
Transgender Men	oestradiol	left anterior superior	0.50	.007
Transgender Men	oestradiol	left posterior	0.94	.592
Transgender Men	oestradiol	left tubular inferior	0.54	.073
Transgender Men	oestradiol	left tubular superior	0.34	.027
Transgender Men	oestradiol	right anterior inferior	0.94	.293

Transgender Men	oestradiol	right anterior superior	0.72	.301
Transgender Men	oestradiol	right posterior	0.65	.153
Transgender Men	oestradiol	right tubular inferior	0.684	.154
Transgender Men	oestradiol	right tubular superior	0.50	.08

Note. SDI 1 = dyadic sexual desire; ROI = regions of interest. Values represent F- and p-values for the interaction measurement x age x hormone x hypothalamic ROI volume from liner mixed models.

Solitary sexual desire (SDI 2) in Transgender Men

In TM, results for solitary sexual desire (SDI 2) across the 12 hypothalamic regions of interest are summarised in Table 10. For testosterone, the interaction between measurement, age, testosterone level and hypothalamic ROI volume was statistically significant for both the left and right whole hypothalamus (whole left: F = 4.72, *p =.024*; whole right: F = 5.01, *p =.020*). Significant interaction effects were also observed for several subunits, including the left anterior inferior (F = 4.18, *p =.035*), left anterior superior (F = 7.46, *p =.005*), left tubular inferior (F = 4.72, *p =.024*), left tubular superior (F = 5.61, *p =.014*), right anterior inferior (F = 6.58, p = *008*), right tubular inferior (F = 4.59, p =*.025*) and right tubular superior (F = 7.39, *p =.006*). For oestradiol, the interaction term was not statistically significant for the left and right whole hypothalamus (whole left: F = 2.48, *p =.112*; whole right: F = 2.45, *p =.114*) or for most hypothalamic subunits (e.g., left anterior inferior: F = 1.71, *p =.209*; left posterior: F = 0.54, *p =.592*; right tubular inferior: F = 2.05, *p =.154*). Significant interaction effects were observed for the left anterior superior (F = 6.75, *p =.007*) and left tubular superior (F = 4.48, *p =.027*) subunits.

Table 10: Effects of sex hormone levels and hypothalamic ROI volume on solitary sexual desire (SDI 2) in transgender men.

Group	Hormone	ROI	*F-value*	*p-value*
Transgender Men	testosterone	whole left	4.72	.024
Transgender Men	testosterone	whole right	5.01	.02
Transgender Men	testosterone	left anterior inferior	4.18	.035
Transgender Men	testosterone	left anterior superior	7.46	.005
Transgender Men	testosterone	left posterior	2.38	.124

Transgender Men	testosterone	left tubular inferior	4.72	.024
Transgender Men	testosterone	left tubular superior	5.61	.014
Transgender Men	testosterone	right anterior inferior	6.58	.008
Transgender Men	testosterone	right anterior superior	2.73	.095
Transgender Men	testosterone	right posterior	2.93	.081
Transgender Men	testosterone	right tubular inferior	4.59	.025
Transgender Men	testosterone	right tubular superior	7.39	.006
Transgender Men	oestradiol	whole left	2.48	.112
Transgender Men	oestradiol	whole right	2.45	.114
Transgender Men	oestradiol	left anterior inferior	1.71	.209
Transgender Men	oestradiol	left anterior superior	6.75	.007
Transgender Men	oestradiol	left posterior	0.54	.592
Transgender Men	oestradiol	left tubular inferior	3.04	.073
Transgender Men	oestradiol	left tubular superior	4.48	.027
Transgender Men	oestradiol	right anterior inferior	1.31	.293
Transgender Men	oestradiol	right anterior superior	1.29	.301
Transgender Men	oestradiol	right posterior	2.08	.153
Transgender Men	oestradiol	right tubular inferior	2.05	.154
Transgender Men	oestradiol	right tubular superior	2.93	.08

Note. SDI 2 = solitary sexual desire; ROI = regions of interest. Values represent F- and p-values for the interaction measurement x age x hormone x hypothalamic ROI volume from liner mixed models.

Discussion

Summary of main findings

The present study investigated the effects GAHT over approximately four months on sexual desire and hypothalamic volume in TM and TW. Based on a biopsychosocial framework of sexual desire, the study focused on the effect of continuous GAHT over four months on dyadic and solitary sexual desire as assessed with the SDI and on hypothalamic volume as a neurobiological correlate of endocrine influences on sexual desire.

In both transgender groups, GAHT produced the expected alterations in circulating sex steroids and was accompanied by divergent trajectories of sexual desire. TM showed a significant increase in both dyadic and solitary sexual desire, while TW demonstrated modest group-level decreases over the same period. At the neuroanatomical level, hypothalamic volume moderated the relationship between hormonal changes and sexual desire.

Linear mixed models revealed that sex hormone levels were associated with sexual desire in a group-specific manner. In TW, oestradiol, but not testosterone, showed significant interactions with time and age predicting both dyadic and solitary sexual desire, suggesting age-dependent effects of feminising oestradiol exposure on sexual desire. By contrast, in TM, testosterone, rather than oestradiol, emerged as the more consistent hormonal correlate of dyadic and solitary desire.

Further exploratory analyses suggested that hypothalamic volume moderated several associations between sex steroids and sexual desire in a hormone- and group-specific manner. In TW, oestradiol-related interactions with hypothalamic volume were significant across most regions of the hypothalamus, whereas testosterone-related interactions remained largely insignificant. This patterns aligns with findings from studies in cisgender women demonstrating that oestradiol is particularly associated with sexual motivation and responsiveness during periods of pronounced endocrine fluctuations, whereas testosterone shows weaker and less consistent associations with sexual desire (Cappelletti & Wallen, 2016; Dennerstein et al., 2002). The opposite pattern emerged in TM: testosterone-related interactions with hypothalamic volume were significant for the whole left and right hypothalamus and for several anterior and tubular subunits, while oestradiol-related interactions were sparse and confined to a small subset of regions. This suggests that androgen-driven hypothalamic plasticity may be a key mechanism by which hormonal shifts translate into changes in both dyadic and solitary desire in this group.

Taken together, these findings partially support the a priori hypotheses, demonstrating that GAHT is accompanied by pronounced, group-specific changes in sexual desire, as well as

hormone-dependent moderation effects of hypothalamic volume. Overall, the present results underscore that early changes in sexual desire during GAHT are closely tied to group-specific endocrine profiles and their interaction with hypothalamic morphology.

Hormonal influences on sexual desire in transgender men

In TM, it was hypothesised that a concurrent increase in testosterone and decrease in oestradiol following GAHT would be associated with higher dyadic and solitary sexual desire (H1a, H1b). It was also hypothesised that these hormone-desire associations would be moderated by changes in hypothalamic volume (H2c, H2d). At a descriptive level, TM showed significant increases in both dyadic and solitary SDI scores over the four-month period, of GAHT which is consistent with previous studies that have reported increases in sexual desire after initiation of virilising hormone therapy in TM (Defreyne et al., 2020; Wierckx et al., 2011). This pattern suggests that exposure to high-dose testosterone, combined with suppression of endogenous oestradiol, generally promotes sexual desire in the early phase of masculinising treatment. As the present follow-up covered only four months of masculinising GAHT, it remains unclear whether the observed increases in sexual desire stabilise, further increase or diminish over longer treatment periods, although previous studies suggest that the most pronounced changes occur in the first 3-6 months and may then plateau (Defreyne et al., 2020; Van Dijk et al., 2019).

The linear mixed models provided a clearer picture of the relationship between sex steroids and changes in sexual desire.Testosterone emerged as a more consistent hormonal correlate of sexual desire than oestradiol across the set of models for SDI 1 and SDI 2 scores, suggesting that sexual desire in TM undergoing masculinising treatment is more closely linked to androgen levels than oestradiol levels. However, these associations were not constantly strong, which is consistent with threshold models suggesting that androgens support sexual desire up to a certain point, whereas variation within or slightly above the physiological range explains only part of the variability in dyadic and solitary desire (Bancroft, 2005; Wierckx, Elaut, et al., 2014). The comparatively weaker and non-significant effects of oestradiol on desire in TM further suggest that peripheral reductions in oestradiol levels are unlikely to be the main cause of increased sexual motivation during early GAHT. Overall, these findings indicate that testosterone plays a significant role in increasing sexual desire in TM, although other aspects, such as psychological and relational factors, still need to be considered, as discussed in Section 5.5. In statistical terms, the significant associations between testosterone and dyadic and solitary desire reject the null hypothesis ($H0_1$) for TM and are consistent with the directional hypotheses H1a and H1b.

Moderator analyses emphasise that the relationship between hormonal changes and sexual desire is influenced by hypothalamic volume. Interaction terms involving testosterone and hypothalamic ROI volume were significant for both dyadic and solitary SDI scores, for the left and right whole hypothalamus, and for several anterior and tubular subunits. In contrast, oestradiol-related interactions were restricted to two left-sided regions: the left anterior superior and left tubular superior subunits. This pattern suggests that changes in sexual desire related to GAHT in TM depend not only on circulating testosterone levels, but also on changes in the volume of hypothalamic structures sensitive to hormones, a point elaborated on in more detail in Section 5.4

Hormonal influences on sexual desire in transgender women

The primary hypothesis for TW posited a concurrent decrease in testosterone and increase in oestradiol following GAHT would be associated with reduced dyadic as well as solitary sexual desire, and that these hormone – desire associations would be moderated by changes in hypothalamic volume (H2c, H2d). This expectation takes into account the endocrine starting point in TW, which more closely resembles that of cisgender men than cisgender women, with testosterone levels typically within the male physiological range before treatment (Hembree et al., 2017). Because feminising GAHT aims to suppress testosterone to low concentrations, and androgens are considered to support sexual desire, a decrease in sexual desire during the early treatment phase was expected (Bancroft, 2005).

At a descriptive level, TW showed modest decreases in both dyadic and solitary SDI scores. This pattern is broadly consistent with longitudinal studies (Defreyne et al., 2020; Van Dijk et al., 2019; Wierckx, Van Caenegem, et al., 2014) reporting reductions in sexual desire during the first months of feminising GAHT, particularly in treatment contexts characterised by pronounced testosterone suppression. Although long-term trajectories appear more heterogenous, previous work (Defreyne et al., 2020; Van Dijk et al., 2019) indicates that the most pronounced endocrine and sexual desire-related changes typically occur within the first 3-6 months and may subsequently stabilise. Given that the present follow-up spanned four months, it remains unclear whether the observed decreases in sexual desire persist, plateau, or partially rebound over longer treatment durations.

A key interpretive question concerns the extent to which evidence from cisgender women can be mapped onto TW. Research in cisgender women suggests that oestradiol shows small positive associations with sexual desire across menstrual cycle, whereas endogenous testosterone is not consistently predictive (Roney & Simmons, 2013). Moreover, menopause-

related declines in oestradiol have been linked to reductions in sexual desire, and hormone replacement therapy with oestrogen was shown to increase desire in postmenopausal women (Cappelletti & Wallen, 2016; Dennerstein et al., 2002; Dow et al., 1983). However, these findings are not directly transferable to TW because the endocrinological context differs fundamentally: menopause primarily reflects a decline in oestradiol in individuals with a female-typical reproductive endocrine history (Dennerstein et al., 2002), whereas feminising GAHT in TW involves medically induced androgen suppression from an initially male-typical baseline combined with exogenous oestradiol exposure. Accordingly, increases in oestradiol in TW, when observed in the context of pronounced testosterone suppression, should not be interpreted as implying an a priori increase in sexual desire.

The linear mixed models provided a more nuanced characterisation of the relationship between sex steroids and changes in sexual desire in TW. Across models for SDI 1 and SDI 2, oestradiol emerged as the more consistent endocrine correlate of dyadic and solitary desire, whereas testosterone effects were largely non-significant. In statistical terms, the significant associations involving oestradiol are consistent with the directional hypotheses (H1c, H1d) for TW and argue against a null model assuming no hormone–desire association. The limited additional contribution of testosterone in the TW models is compatible with threshold accounts suggesting that androgens support sexual desire only up to a minimal level, such that once testosterone levels are strongly suppressed, residual variation explains little additional variance in dyadic or solitary desire (Bancroft, 2005). Taken together, these findings indicate that endocrine predictors of early changes in sexual desire in TW are best understood against the backdrop of a treatment□induced shift from a male□typical hormonal baseline, rather than by direct analogy to endocrine mechanisms described in cisgender women.

Moderator analyses further indicated that hypothalamic volume shaped hormone –desire associations in TW. Interaction terms involving oestradiol and hypothalamic ROI volume were significant for dyadic sexual desire across all ROIs and for solitary desire across most ROIs, whereas testosterone–related interactions were largely absent. This pattern suggests that interindividual differences in hypothalamic morphology may be relevant for how strongly endocrine changes relate to subjective sexual desire during early feminising treatment. These findings align with evidence that GAHT can be associated with structural plasticity in the hypothalamus (Konadu et al., 2023b; Kranz et al., 2018; Pol et al., 2006). At the same time, this interpretation must remain strictly structural. Hypothalamic volume reflects morphology and cannot be equated with functional activation or neural responsivity. Thus, the present results

support a moderation role of hypothalamic morphology in hormone–desire coupling, while leaving questions about underlying functional mechanisms for future research.

Taken together, the present findings indicate that early feminising GAHT in TW is accompanied by modest reductions in dyadic and solitary sexual desire, consistent with the expectation that suppressing testosterone can attenuate sexual desire (Bancroft, 2005). Finally, hypothalamic morphology appeared to moderate these associations, suggesting that structural differences in the hypothalamus may contribute to variability in early treatment–related changes in sexual desire.

The neuroanatomical implications of these results are discussed in the following section, "Hypothalamic volume as a potential moderator of hormone-desire associations".

Hypothalamic volume as a potential moderator of hormone-desire associations

The present pattern of findings suggests that the hypothalamus is not only a neural target of GAHT, but also moderates the strength of the associations between GAHT-related changes in sex steroid levels and dyadic as well as solitary sexual desire. In both TM and TW, the predominant GAHT hormone (testosterone in TM and oestradiol in TW) showed volume-dependent associations with SDI scores, with significant interactions emerging primarily in anterior and tubular subregions. Rather than indicating consistent volumetric effects of GAHT, these findings imply that the strength of the relationship between sex hormone levels and sexual desire fluctuates among individuals and is partly determined by interindividual differences in hypothalamic volume. This pattern may help to explain why similar masculinising or feminising hormone regimens can result in different changes in sexual desire across individuals, with hypothalamic morphology influencing how strongly sex hormone changes relate to sexual desire. Previous neuroimaging studies have demonstrated that GAHT can alter the structure and microstructure of the hypothalamus (Konadu et al., 2023a; Kranz et al., 2018; Pol et al., 2006). The present findings extend this work by suggesting that these GAHT-sensitive regions of the hypothalamus are relevant to the relationship between circulating sex steroid levels and changes in sexual desire.

In TM, significant testosterone-hypothalamic volume interactions were confined to the left and right whole hypothalamus and several anterior and tubular subunits. In contrast, oestradiol-related interactions were limited to two left-sided regions. This suggests that hypothalamic modulation of sexual desire is predominantly androgen-dependent. This pattern aligns with studies emphasising the anterior hypothalamic nuclei as key integration regions for gonadal steroids, autonomic regulation and motivational processes involved in sexual behaviour

(Campbell & Herbison, 2014; Pfaus, 2009). Human neuroimaging studies have identified the hypothalamus, together with regions such as the ventral striatum, amygdala and anterior cingulate cortex, as part of a network that is reliably engaged during erotic stimulation and subjective sexual desire (Cacioppo, 2017; Cacioppo et al., 2012). Within this framework, the present results build on previous longitudinal studies demonstrating hypothalamic plasticity during masculinising treatment (Kranz et al., 2018, 2020; Pol et al., 2006) by showing that differences in the volume of the anterior and tubular hypothalamic regions are related to the strength of the association between changes in testosterone levels and changes in sexual desire in TM.

A complementary pattern emerged in TW. Here, interaction terms involving oestradiol and hypothalamic volume were significant for most hypothalamic subregions, whereas the corresponding testosterone-related interactions were largely insignificant. This asymmetry aligns with studies indicating that the feminising regimens combining oestradiol with androgen suppression are often associated with reductions in sexual desire, particularly during the early treatment phase (Defreyne et al., 2020; Van Dijk et al., 2019). Furthermore, structural MRI studies suggest that anterior and tubular hypothalamic subunits are especially sensitive to feminising GAHT in TW (Konadu et al., 2023). The present finding extends this structural evidence by suggesting that the hypothalamus represents a central site where feminising endocrine changes and changes in sexual desire converge, adding a behavioural dimension to this structural evidence.

More broadly, the dependence of the relationship between sex hormone levels and sexual desire on hypothalamic volume in both groups is consistent with theoretical models that distinguish organisational from activational effects of sex steroids on hypothalamic circuits (Lenz & McCarthy, 2010; Schulz & Sisk, 2016). Organisational influences shape the basic architecture and receptor distribution of hypothalamic networks during sensitive developmental periods (Lenz & McCarthy, 2010; McCarthy, 2008). In contrast, activational effects in adulthood can induce reversible plasticity within these networks in response to changing hormonal environments (Campbell & Herbison, 2014). Within this framework, the present moderation effects suggest that GAHT may interact with pre-existing and potentially plastic volumetric differences in hypothalamic subregions, such that these structural characteristics modulate the strength with which changes in sex steroid levels are expressed as changes in sexual desire. In line with neuroimaging-based models of the "sexual brain" which position the hypothalamus within a network linking bodily states, reward processing and subjective sexual desire (Bancroft, 2005; Cacioppo, 2017; Cappelletti & Wallen, 2016; Pfaus, 2009), the current

findings support the idea that hypothalamic morphology acts as a hormone-sensitive contextual factor shaping the motivational impact of masculinising and feminising hormone regimens, thereby helping to explain the heterogeneous trajectories of sexual desire observed during GAHT, rather than reflecting a passive structural consequence of GAHT alone.

Psychosocial interpretation of changes in dyadic and solitary sexual desire

The present findings marked increases in both dyadic and solitary sexual desire in TM, and modest group-level decreases in dyadic desire, along with less pronounced changes in solitary desire in TW, fit well within biopsychosocial models of sexual desire. These models conceptualise desire as the outcome of interacting biological, psychological and relationship factors rather than a simple reflection of circulating sex steroid levels (Carvalho & Nobre, 2010, 2011; Dosch et al., 2016; Levine, 2002, 2003). In this perspective, GAHT changes the endocrine milieu but simultaneously alters body image, gender congruence, mood, self-esteem, and relationship dynamics, which together shape dyadic and solitary sexual desire in complex ways. Previous work has shown that cognitive-emotional factors (such as dysfunctional sexual beliefs and lack of erotic thoughts) and relationship variables (e.g. cohesion, affection) are among the strongest predictors of sexual desire (Carvalho & Nobre, 2010, 2011).

In this light, the marked increases in dyadic and solitary sexual desire in TM are unlikely to be purely androgen driven. They are plausibly linked to reductions in GD and negative thoughts, together with improvements in body image and sexual self-confidence (Dosch et al., 2016; Fisher et al., 2016; Van Leerdam et al., 2023), all of which would be expected to facilitate higher desire scores. Conversely, the change in desire in TW does not simply fit the expectation that greater gender congruence should increase sexual desire. Within the cognitive-emotional framework (Carvalho & Nobre, 2010, 2011), this pattern may reflect that during the first months of feminising GAHT, the positive effects of gender affirmation are still counterbalanced by heightened self-consciousness about bodily changes and uncertainty about partner reactions and relationship strain, a combination that is likely to foster negative or ambivalent sexual thoughts (Carvalho & Nobre, 2010, 2011). Cognitive-emotional contexts of this kind, have been identified as central correlates of reduced sexual desire (Carvalho & Nobre, 2010, 2011), so the present findings illustrate how endocrine, cognitive and relationship factors can act in opposing directions in the initial months of transition, particularly in TW.

In line with this, sexual desire has been conceptualised as a motivational state that reflects the balance of forces that pull an individual toward and push them away from sexual activity across the lifespan (Levine, 2002, 2003). These forces include biological drives, cognitive-affective

processes, relationship dynamics and sociocultural influences, which together determine whether sexual stimuli are experienced as salient, rewarding and worth pursuing (Levine, 2002, 2003). Applied to the present findings, the robust increases in dyadic and solitary sexual desire in TM can be interpreted as a change in the overall motivational balance, with sexual desire becoming mire approach-oriented rather than avoidance-driven. Rising testosterone, reduced GD and improved body image likely strengthen the "pull" towards sexual activity while weakening avoidance-related forces. In TW, by contrast, the modest decrease in dyadic desire alongside relatively small changes in solitary desire suggests that, during the first months of feminising GAHT, positive effects of gender affirmation are still offset by self-consciousness and negative sexual cognitions, in a way that approach- and avoidance-related forces remain more finely balanced.

Taken together, the present findings underscore that GAHT-related changes in sexual desire cannot be understood in endocrine terms alone, but need to be viewed within a broader biopsychosocial framework in which hormonal shifts interact with cognitive and emotional factors.

Limitations and Future Directions

Some limitations of the present study need to be addressed. First, the sample size was small, and the two groups were not balanced. Consequently, the statistical power was reduced particularly with regard to detecting higher-order interactions and region-specific effects in the hypothalamus. Therefore, results remain preliminary and await further validation from replication studies in considerably larger samples. Furthermore, there were only two measurement points available over a period of approximately four months. This limited follow-up period only captures the early phase of gender-affirming hormone therapy, which means that firm conclusions about long-term changes in sexual desire or hypothalamic volume cannot be drawn. Previous studies have shown that TM tend to experience the most significant changes in sexual desire within the first few months of treatment, after which desire appears to stabilise (Defreyne et al., 2020; Van Dijk et al., 2019). However, longer observation periods are required to determine whether the observed trajectories persist, increase or decrease over time.

Moreover, while the discussion was based on biopsychosocial models, the study did not directly evaluate important psychological factors that are recognised to affect sexual desire, including cognitive and emotional variables, relationship quality, and broader contextual determinants (Carvalho & Nobre, 2010, 2011; Dosch et al., 2016).

In addition, all data on sexual desire were based on self-report. As sexual desire is a highly private and subjective experience, responses to questionnaires are susceptible to recall bias, social desirability, and discomfort when disclosing intimate information. This may have introduced noise and attenuated the associations with hormonal and neural measures (Levine, 2002, 2003). The methodological constraints of the neuroimaging approach also warrant caution. The hypothalamus is a small structure located near the ventricles, and volumetric estimates based on automated segmentation are susceptible to partial volume effects and segmentation error. Nevertheless, the FreeSurfer-based parcellation employed here aligns with current neuroimaging standards and has been effectively applied in prior studies examining hypothalamic structure in relation to GAHT (Konadu et al., 2023; Kranz et al., 2018). Subregional findings in particular should be considered preliminary and require confirmation through higher-resolution imaging and additional analytical methods (Neudorfer et al., 2020). Future research should aim to recruit larger and more balanced samples of transgender individuals, extend the follow-up period beyond the early months of hormone treatment and conduct a broader assessment of sexuality. Integrating psychosocial measures, such as body image, relationship status and functioning, stress and social cognitions, with endocrine profiles and high-resolution neuroimaging, would enable a more thorough testing of the biopsychosocial framework outlined in this study. This would also help clarify how hormonal, neural, and psychosocial processes collectively influence the development of solitary and dyadic sexual desire after GAHT.

Conclusion

GAHT seems to have a considerable impact on sexual desire in transgender individuals. Over the four moths of high-dose treatment, TM typically show marked increases in both dyadic and solitary sexual desire, whereas TW tend to experience modest reductions, indicating directionally distinct motivational shifts under masculinising versus feminising regimens. These changes appear to arise form interactions between sex steroid concentrations, hypothalamic plasticity and psychosocial adaptions, rather than from endocrine factors alone. This supports a biopsychosocial perspective in which hormonal, neural and contextual processes jointly shape GAHT-related trajectories of sexual desire across transition.

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AIC = Akaike Information Criterion

DSM = Diagnostic and Statistical Manual of Mental Disorders

GAHT = Gender-affirming hormone therapy

GD = Gender Dysphoria

ICD = International Classification of Diseases

LMM = Linear mixed models

MRI = Magnetic Resonance Imaging

PET = Positron Emission Tomography

REML = Restricted Maximum Likelihood

ROI = Region of Interest

SCID = Structured Clinical Interview

SDI = Sexual Desire Inventory

SSRIs = Selective Serotonin Reuptake Inhibitors

TM = Transgender men

TW = Transgender women

WHO = World Health Organization

WPATH = World Professional Association for Transgender Health