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INTERSTITIAL HYPOTHALAMIC NUCLEI III (INAH-3) AND GENDER IDENTITY: AN INTEGRATIVE REVIEW OF NEUROBIOLOGICAL EVIDENCE

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Abstract: Gender identity, as a biopsychosocial construct, has been the subject of intense neuroscientific research in recent decades. This article consists of an integrative review of the literature with the aim of compiling and critically analyzing the evidence on the relationship between the Interstitial Hypothalamic Nuclei III (INAH-3) and gender identity. The search was conducted in the PubMed, Scopus, SciELO, and LilaCs databases, covering the period from January 2000 to February 2026. Twenty-two studies were selected, including postmortem, structural and functional neuroimaging, genetic, animal model, and systematic review studies, organized into five thematic categories: (1) Classical Morphological Evidence; (2) Functional and Connectivity Evidence; (3) Animal Models; (4) Genetic, Epigenetic Evidence, and Integrative Reviews; and (5) Critical, Clinical, and Social Perspectives. The results confirm the INAH-3 as the most robust structure of sexual dimorphism in the human brain, with significantly greater volume and number of neurons in cisgender men. In transgender individuals, particularly trans women (assigned male at birth who identify as women), a complete structural reversal of the INAH-3 is observed, resembling the female pattern, regardless of circulating hormones in adulthood. Studies of functional connectivity and white matter microstructure complement these findings, revealing unique neural signatures in trans individuals. Animal models with the Sagittal Nucleus of the Hypothalamus (SGN) provide functional support for the hypothesis of early hormonal organization. Critical analysis of the methodology points to limitations inherent in postmortem studies, such as small sample sizes and difficulty in controlling for confounding variables. It is concluded

that INAH-3 is a central component of a broader neural network involved in gender identity, whose organization occurs early in development, possibly through hormonal and epigenetic mechanisms. The integration of this evidence reinforces the need for a multidisciplinary, ethical, and non-pathologizing approach to the health care of people with diverse gender identities.

Keywords: INAH-3. Hypothalamus. Gender Identity. Transgender People. Sexual Dimorphism. Neurobiology.

INTRODUCTION

Understanding the neurobiological mechanisms underlying gender identity is one of the most fascinating and complex challenges in contemporary neuroscience. Gender identity, defined as a person's internal and individual experience of gender, which may or may not correspond to the sex assigned at birth (BUTLER, 2003), emerges from the dynamic interaction between genetic, hormonal, epigenetic, and environmental factors. In recent decades, the anterior hypothalamus has established itself as a brain region of central interest for this research, due to its fundamental role in neuroendocrine regulation and reproductive and social behaviors (SWAAB, 2003).

Within this region, the Interstitial Nuclei of the Anterior Hypothalamus (INAH 1-4) were initially described by Allen et al. (1989) as candidates for homology with the sexually dimorphic nucleus of the preoptic area (SDN-POA) of rodents, identified by Gorski et al. (1978). Among these four nuclei, INAH-3 emerged as the most robust and replicable marker of sexual dimorphism in the human brain. Systematic morphometric studies, such as those pre-

sented in Table 1, have shown that INAH-3 is significantly larger in volume and contains a substantially greater number of neurons in men than in women, a difference that persists even after controlling for variables such as brain weight and age (BYNE et al., 2000). Figure 1 illustrates this dimorphism comparatively, highlighting the specificity of the INAH-3 in contrast to the other interstitial nuclei.

The relationship between this structure and gender identity gained prominence from the seminal study by Garcia-Falgueras and Swaab (2008). When analyzing the uncinate nucleus (which comprises INAH-3 and INAH-4) in postmortem brains, the authors made a crucial discovery: trans women (individuals assigned male at birth but who identify as women) had a volume and number of neurons in INAH-3 that corresponded to the typical pattern of cisgender women, not men. This revolutionary finding suggested that gender identity has a structural correlate in the brain, possibly established during prenatal development, and that it can be dissociated from biological sex and sexual orientation.

At the same time, animal models have provided functional support for these observations. The identification of the Sagittal Nucleus of the Hypothalamus (SGN) in rats by Mori et al. (2009) revealed a sexually dimorphic interstitial structure located between the arcuate and ventromedial nuclei, whose morphology can be permanently “masculinized” by neonatal testosterone administration. Subsequent functional studies, such as those detailed in Table 3, have demonstrated that the SGN is activated during sexual behavior and in response to hormonal and sensory cues in both males and females, reinforcing its integrative role in

the neural circuits of reproduction and, potentially, identity (MATSUDA et al., 2017; BALABANOV et al., 2018).

However, advances in neuroimaging techniques over the past two decades have allowed research to expand beyond the static morphology of isolated nuclei. Studies using Diffusion Tensor Imaging (DTI) and ultra-high field functional magnetic resonance imaging (7 Tesla), summarized in Table 2, have revealed that gender identity also manifests itself in unique patterns of white matter structural connectivity (KRANZ et al., 2014) and in complex functional networks, such as those underlying empathy (SPIES et al., 2016). Additionally, genetic and epigenetic research, organized in Table 4, has identified variants and mechanisms that may influence the developmental trajectory of these structures (JAIN; RANA, 2021; SARI et al., 2024; ALAGHA et al., 2025).

Despite the consistency of the findings, the field is not without controversy and methodological challenges. Distinct theoretical perspectives, such as the personalist view presented by Rivarola Espinoza (2008) and the discussions on depathologization compiled in Table 5, question purely biological interpretations and emphasize the importance of psychosocial factors, stigma, and social context in the overall health of sexual and gender minorities (BACK et al., 2019; BHUGRA et al., 2022).

Considering the above, this research was guided by the following question: what scientific evidence, produced between 2000 and 2025, exists on the structural and functional association of INAH-3 with gender identity, and what is the methodological quality of these findings?

The overall objective of this integrative review was to compile and critically analyze the scientific evidence on the relationship between the INAH-3 and gender identity. The specific objectives were: (1) to identify the structural (volume, number of neurons, microstructure) and functional (connectivity) patterns of the INAH-3 and associated neural networks in individuals with different gender identities; (2) to assess the methodological quality of the included studies, considering confounding variables such as adult hormones, comorbidities, and sample selection criteria; and (3) to propose, based on critical analysis, gaps and future directions for research and neurobiological investigation of gender identity. The relevance of this study lies in the need to synthesize a rapidly expanding body of knowledge, offering an integrated and critical view that can inform both future research and clinical practices and public policies based on evidence and respect for human rights.

METHODOLOGY

This is an integrative literature review, a method that allows for the synthesis and critical analysis of multiple studies with different designs, enabling a broad and in-depth understanding of a complex phenomenon (SOUZA; SILVA; CARVALHO, 2010). The bibliographic survey was conducted between November 2025 and February 2026, in the electronic databases PubMed (National Library of Medicine), Scopus, SciELO (Scientific Electronic Library Online), and Lilacs (Latin American and Caribbean Health Sciences Literature).

The search strategy combined health sciences descriptors (DeCS/MeSH) and relevant keywords, using Boolean operators.

The search string applied was: (“INAH-3” OR “Interstitial Nucleus of the Anterior Hypothalamus 3” OR “sexually dimorphic nucleus” OR “uncinate nucleus” OR “sagittalis nucleus”) AND (“gender identity” OR “transsexualism” OR “transgender persons” OR “gender dysphoria” OR “sexual orientation”).

Studies that met the following criteria were included: (a) original articles (experimental, observational) or review articles (systematic, integrative, or narrative); (b) published between November 2025 and February 2026; (c) available in Portuguese, English, or Spanish; (d) that directly addressed the morphology, development, histology, genetics, or functional correlation of the INAH-3 or analogous hypothalamic structures with gender identity or sexual dimorphism in humans. Studies with animal models were included only when they discussed homologous structures (such as the SGN) to provide functional support for findings in humans, but they did not constitute the main corpus of the analysis on gender identity.

The study selection process was carried out in three stages. In the first stage, the titles and abstracts of all identified records were screened, with duplicates removed and articles clearly outside the scope excluded. In the second stage, the preselected studies were read in full to assess their eligibility based on the inclusion criteria. Finally, data from the included studies were extracted and organized into five synoptic tables, corresponding to the thematic categories defined a posteriori: (1) Classical Morphological Evidence (INAH-3); (2) Functional and Connectivity Evidence; (3) Animal Models (SGN); (4) Genetic, Epigenetic Evidence, and Integrative Reviews; and (5) Criti-

cal, Clinical, and Social Perspectives. Each table contains the following information: authors, year of publication, objective, research design, sample characterization, main techniques used, and main results. Data analysis was predominantly descriptive and critical, integrating findings from different categories to construct the discussion.

RESULTS

The initial search strategy retrieved 283 records. After removing duplicates ($n=71$), 212 studies were screened by title and abstract, resulting in the exclusion of 173 for not addressing the central theme. Thus, 39 articles were read in full, of which 17 were excluded because they did not meet the inclusion criteria (e.g., reviews without primary data on INAH-3, studies exclusively with animals without correlation with human gender identity, or articles focused only on sexual orientation). The final sample of this integrative review consisted of 22 studies, organized in the following five tables.

DISCUSSION

This integrative review consolidates a robust and multifaceted body of evidence indicating that INAH-3 is a fundamental neuroanatomical structure for understanding gender identity. The analysis of the 22 selected studies, organized into the five thematic categories in Tables 1 to 5, allows for a structured discussion, complemented by the illustration in Figure 1.

INAH-3 as a Marker of Sexual Dimorphism: Robustness and Specificity

The confirmation of the sexual dimorphism of INAH-3, replicated by multiple studies using rigorous methodologies, is the foundation on which research on gender identity is based. The work of Byne et al. (2000), detailed in Table 1, is fundamental in this regard, as it used advanced stereological techniques on carefully selected post-mortem samples to demonstrate that the volume of INAH-3 is approximately 50% greater in men, a difference attributable to a total number of neurons that is about 60% higher. The absence of differences in neuronal size or packing density suggests that dimorphism is established during neurodevelopment, probably by mechanisms that influence neuronal survival, migration, or differentiation, rather than by cellular hypertrophy in adulthood.

This finding not only corroborated the seminal work of Allen et al. (1989) and Le-Vay (1991), but also refined it by demonstrating the specificity of INAH-3. As Byne et al. (2001) reiterated in the same context, other nuclei, such as INAH-1 and INAH-2, do not show consistent dimorphism, which consolidates INAH-3 as the main sexually dimorphic nucleus of the human anterior hypothalamus. Figure 1 clearly illustrates this specificity, contrasting the marked sexual difference in INAH-3 with the absence of significant differences in the other nuclei. This specificity is crucial because it allows us to distinguish the role of INAH-3 from other structures, such as SDN-POA (INAH-1), which, according to Swaab (2003), also in Table 1, is more related to other aspects of hypothalamic function and does not show variation associated with sexual orientation.

AUTHOR(S) AND YEAR	OBJECTIVE	DESIGN/SAMPLE	MAIN RESULTS
BYNE et al. (2000)	Investigate sexual dimorphism in INAH 1-4	Post-mortem, stereology. 18 men, 20 women	INAH-3: 50% greater volume and 60% more neurons in men. Single dimorphic nucleus.
BYNE et al. (2001)	Analyze variations by sex, sexual orientation, and HIV	Post-mortem. 34 heterosexual men, 34 women, 14 homosexual men (all HIV+)	Confirmed INAH-3 dimorphism. No difference between heterosexual and homosexual men in the number of neurons. INAH-1 increased in HIV+.
GARCIA-FALGUE-RAS; SWAAB (2008)	Relating INAH-3 to gender identity	Post-mortem. 14 cisgender men, 11 cisgender women, 10 trans women (MtF), 1 trans man (FtM)	Structural reversal in trans women: INAH-3 with volume and number of neurons equal to that of cisgender women. Independent of adult hormones.
SWAAB (2003)	Review evidence on SDN-POA/ INAH-1	Book chapter – review	Clarifies nomenclature. INAH-1 (SDN-POA) is not related to sexual orientation, unlike INAH-3.

Table 1 – Classic Morphological Evidence on INAH-3

Source: Authors, 2026.

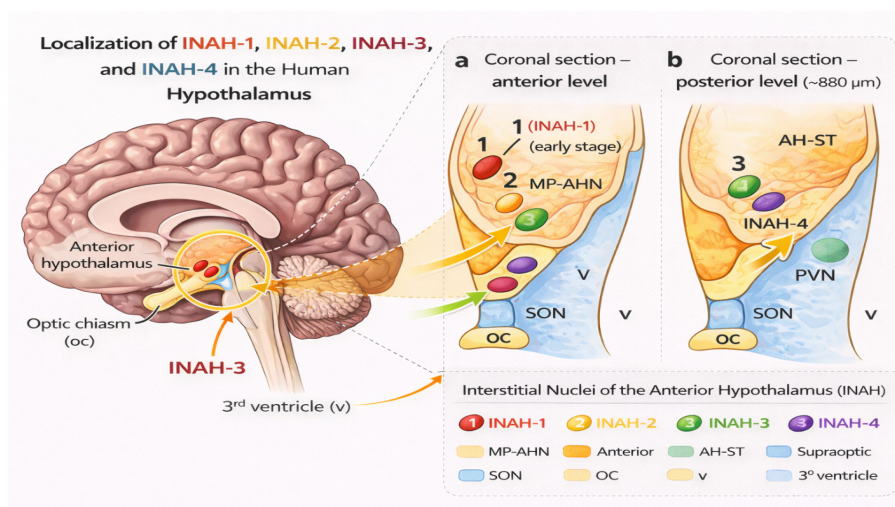


Figure 1: 80-micrometer-thick coronal sections of specimen ms136 (presumed heterosexual male, 69 years old) illustrate the INAH, indicated by the corresponding numbers. INAH1 and INAH2 are clearly visible at level a, where INAH3 begins to emerge as an area of greater density within the MP-AHN. Level b is 880 mm posterior to level a, and in it INAH3 and INAH4 are prominent. INAH3 is in close proximity to a cell group designated by Bleier as AH-ST (see Byne, 1998, for discussion). The abbreviations used are: AH-ST, confluence of the anterior hypothalamic nucleus (AH) with the nucleus of the bed of the terminal stria (ST); MP-AHN, medial preoptic anterior hypothalamic nucleus; PVN, paraventricular nucleus; oc, optic chiasm; SON, supraoptic nucleus; and v, third ventricle. The data demonstrate robust sexual dimorphism specifically in INAH-3, with higher volume and number of neurons in males. Source: Image adapted from Byne et al. (2001).

AUTHOR(S) AND YEAR	OBJECTIVE	DESIGN/SAMPLE	MAIN RESULTS
KRANZ et al. (2014)	Investigate white matter microstructure in transgender individuals	DTI. 23 trans men (FtM), 21 trans women (MtF), 22 cisgender men, 23 cisgender women (without hormones)	Continuous transition in mean diffusivity: cisgender women > trans men > trans women > cisgender men. Distinct neuroanatomical signature prior to hormones.
SPIES et al. (2016)	Evaluate neural networks of empathy during gender transition	Longitudinal 7T rs-fMRI. 24 trans women (MtF), 33 trans men (FtM) (4 weeks and 4 months of hormones)	Trans women: lower baseline connectivity in the SMG; increased with hormones, approaching cisgender levels. Correlation with emotional improvement.
LUTHER et al. (2021)	Influence of gender roles and sexual attraction on facial categorization	Experimental. 34 women, 33 men. Morphed faces (0-140%)	Biological sex did not influence. Gender roles and sexual attraction were significant predictors. Replicates “male bias.”

Table 2 – Functional and Connectivity Evidence

Source: Authors, 2026.

AUTHOR(S) AND YEAR	OBJECTIVE	DESIGN/SAMPLE	MAIN RESULTS
MORI et al. (2009)	To describe and characterize the SGN in rats	Neuroanatomical, immunohistochemistry (ER α , calbindin)	SGN: structure between ARC and VMH. Dimorphic (1.7x larger in males). Masculinizable by neonatal testosterone.
MATSUDA et al. (2017)	Investigate SGN activation during sexual behavior in males	Experimental, c-Fos. Groups: naive, sniffing, mount, intromission, ejaculation	Activation of the SGN in the appetitive phase (sniffing), peak in mount. Role in sexual motivation, not in consummation.
BALABANOV et al. (2018)	Investigate SGN activation in females after hormonal manipulation	Experimental, c-Fos in ovariectomized rats with hormones and mating	SGN activated by estradiol+progesterone and additionally by mating. Responds to motivational and consummatory phases.

Table 3 – Animal Models: The Sagittal Nucleus of the Hypothalamus (SGN)

Source: Authors, 2026.

AUTHOR(S) AND YEAR	OBJECTIVE	DESIGN/SAMPLE	MAIN RESULTS
JAIN; RANA (2021)	To consolidate biological evidence on alternative sexual orientation	Integrative review	INAH-3 is a key finding. It connects genes (Xq28, SLITRK6) to the prenatal hormonal hypothesis. Role of COMT in dopamine.
ALAGHA et al. (2025)	Review biological, genetic, and environmental factors in homosexuality	Narrative review	Multifactorial model: genetics (COMT, MTHFR), epigenetics, FBOE, prenatal hormones. Role of fetal aromatase.
SARI et al. (2024)	Review neurobiological components of sexual identity development	Narrative review	INAH-3 and BSTc as key structures. Discusses brain-genitalia dissociation and epigenetic mechanisms (methylation, XIST).

Table 4 – Genetic, Epigenetic, and Integrative Review Evidence

Source: Authors, 2026.

AUTHOR(S) AND YEAR	OBJECTIVE	DESIGN/SAMPLE	MAIN RESULTS
RIVAROLA ESPINOZA (2008)	Critical review of homosexuality from a personalist perspective	Theoretical essay	Questions LeVay’s studies (samples with AIDS). Defends psychosocial influence and view of “acquired neurosis.”
BACK et al. (2019)	Analyzes discourses on depathologization	Integrative review (2000-2017). 30 publications	Three matrices: essentialist, psychoanalytic, constructionist. Predominant depathologizing trend.
BHUGRA et al. (2022)	Global analysis of the mental health of sexual minorities	Commissioned review (IRP)	Contextualizes neurobiological findings in minority stress (MEYER). Morbidity stems from stigma, not orientation.
ARAÚJO et al. (2022)	Systematize Brazilian publications on gender, sexuality, and aging	Systematic review using IRaMuTeQ. 33 articles (2010-2020)	Gap regarding the elderly LGBTQIAPN+ population. Biomedical focus on STDs, low intersectionality.
SANTANA et al. (2021)	Mapping publications on gender and sexuality in basic education	Systematic review (2015-2021). 12 studies	Weaknesses in teacher training. Biologizing approach, restricted to Science/Biology. Concentration in the Southeast.
SANTOS et al. (2024)	Understanding the body image of transgender people for school physical education	Literature review (Scopus). 5 articles	Lack of studies on the body image of transgender people in the school context. High prevalence of body dissatisfaction.

Table 5 – Critical, Clinical, and Social Perspectives

Source: Authors, 2026.

Structural Reversal of INAH-3 in Transgender People: Evidence of Prenatal Organization

The paradigmatic advance in this area was made by Garcia-Falgueras and Swaab (2008), whose findings are summarized in Table 1. By demonstrating that INAH-3 in trans women (individuals assigned male at birth but who identify as women) does not correspond to their biological sex (male) but rather to their gender identity (female), the authors provided the most direct evidence that gender identity has a neuroanatomical correlate. The complete reversal in the number of neurons, aligning trans women with cisgender women, strongly suggests that this characteristic is established by brain differentiation processes that occur in a critical window of development, probably in the second trimester of pregnancy, when the brain differentiates sexually in a manner dissociated from the genitalia (SWAAB; GARCIA-FALGUERAS, 2009).

Crucially, the authors noted that this pattern is not influenced by cross-hormone therapies or sex reassignment surgeries in adulthood. This is corroborated by neuroimaging studies, such as that by Kranz et al. (2014) in Table 2, which, when investigating the microstructure of white matter in transgender people who had not yet started any hormone treatment, found patterns of connectivity (measured by mean diffusivity) that were on a continuum between typically male and female patterns, evidencing that gender identity manifests itself in a unique neurobiological “signature” that precedes and is independent of circulating hormones in adulthood.

Beyond the Core: Neural Networks, Connectivity, and Social Processing

Modern neuroscience has expanded the analysis beyond the morphology of isolated nuclei, investigating how the INAH-3 and other structures fit into complex neural networks. The study by Spies et al. (2016), in Table 2, using ultra-high field functional magnetic resonance imaging (7 Tesla), revealed that trans women have a distinct pattern of functional connectivity at rest in a network centered on the supramarginal gyrus (SMG), a region associated with empathy and overcoming emotional egocentrism (SILANI et al., 2013). The observation that gender transition and hormone therapy induce changes in this connectivity, bringing it closer to the patterns of cisgender groups, highlights the remarkable plasticity of the adult brain and suggests that gender identity modulates not only deep structures, such as the INAH-3 illustrated in Figure 1, but also higher-order cortical networks.

This functional complexity is complemented by behavioral studies, such as that by Luther et al. (2021), also in Table 2, which demonstrated that the categorization of faces as male or female is influenced not by the biological sex of the observer, but by their internalized gender roles and sexual attraction. This finding highlights that gender processing is a multifaceted phenomenon involving the interaction between basic perceptual systems, subcortical structures (such as the INAH-3), and cognitive and social schemas shaped by individual experience.

Animal Models: Functional Support for Hypothalamic Organization

Research with animal models, although with the necessary caveats regarding its

direct applicability to human behavior, offers invaluable functional support for understanding the mechanisms that shape nuclei such as the INAH-3. The discovery of the Sagittal Nucleus of the Hypothalamus (SGN) by Mori et al. (2009), detailed in Table 3, is particularly relevant. Its interstitial location between classical nuclei (arcuate and ventromedial), its sexual dimorphism (greater in males), and its masculinization by neonatal testosterone mimic the characteristics of INAH-3, suggesting a possible functional homology that echoes the human morphological findings illustrated in Figure 1.

The studies by Matsuda et al. (2017) and Balabanov et al. (2018), also in Table 3, go beyond anatomy, demonstrating the functionality of the SGN. Neuronal activation (c-Fos expression) in the SGN of male rats during the early stages of sexual behavior (appetitive) and in female rats in response to ovarian hormones and mating positions this structure as a key integrator of hormonal and sensory signals, possibly orchestrating the transition from motivation to action. These findings in rodents reinforce the hypothesis that interstitial hypothalamic nuclei, such as INAH-3 in humans, are dynamic and central components of the neural circuits that underlie sex- and gender-related behaviors and identities.

Integration into a Multifactorial Model: Genetics, Epigenetics, and the Role of the Environment

The most recent reviews, summarized in Table 4, such as those by Jain and Rana (2021), Alagha et al. (2025), and Sari et al. (2024), are unanimous in placing INAH-3 within a multifactorial explanatory model, which rejects reductionist views of a single

cause. INAH-3 emerges as an anatomical “common final pathway,” whose development is influenced by multiple factors that interact over time. The robustness of this nucleus as a morphological marker, evidenced in Figure 1, is now understood as the result of a complex cascade of molecular and cellular events.

Genome-wide association studies (GWAS), such as that by Ganna et al. (2019), have identified several small-effect loci associated with sexual behavior. The connection with INAH-3 occurs indirectly, through genes such as *SLITRK6*, expressed in the diencephalon (where the hypothalamus originates) (JAIN; RANA, 2021). Other genes, such as *COMT*, involved in dopamine metabolism, and *MTHFR*, linked to DNA methylation, suggest pathways through which genetic variations could influence neurotransmission in reward and affective bonding circuits, or gene expression patterns during development (ALAGHA et al., 2025).

Epigenetics emerges as the molecular bridge that may explain how environmental factors, including prenatal hormonal exposure and stressors, can leave lasting marks on gene expression, modulating the differentiation of nuclei such as INAH-3 (SARI et al., 2024). The hypothesis of failure to remove sex-specific epigenetic marks (RICE et al., 2012) is an attractive model to explain discordance in monozygotic twins, a phenomenon observed in both sexual orientation and gender identity.

Critical, Clinical, and Social Perspectives: Depathologization and Human Rights

The interpretation of neurobiological findings cannot occur in an ethical and social vacuum. Perspectives such as that of Rivarola Espinoza (2008), in Table 5, although anchored in a personalist and conservative view that contrasts with the current scientific consensus, have the merit of raising important questions about the limits of biological determinism and the influence of psychosocial factors. Methodological criticism of LeVay's studies, for example, points to the need for caution in causal interpretation when samples are small or present comorbidities.

The literature on depathologization, summarized by Back et al. (2019) in Table 5, demonstrates a clear historical and scientific trend toward understanding homosexuality and transsexuality as natural variations of human diversity, rather than mental disorders. This view is reinforced by the international commission led by Bhugra et al. (2022), also in Table 5, which, in reviewing the mental health of sexual minorities, concludes that the higher prevalence of psychiatric disorders in this population does not stem from sexual orientation or gender identity itself, but from stigma, discrimination, and minority stress (MEYER, 2003). The unique neural signatures observed in studies such as that by Kranz et al. (2014) should be interpreted in light of this context, as markers of diversity rather than pathology.

Finally, studies in the field of education and aging, such as those by Araújo et al. (2022), Santana et al. (2021), and Santos et al. (2024), presented in Table 5, reveal important gaps in knowledge production

and professional training. The invisibility of the elderly LGBTQIAPN+ population, the fragility of teacher training to deal with gender diversity in schools, and the absence of studies on the body image of transgender people in the context of Physical Education are examples of how neurobiological knowledge needs to be translated and integrated into public policies and affirmative pedagogical practices.

Methodological Limitations and Biases of the Included Studies

Despite the consistency of the findings, the methodological quality of studies on INAH-3 has inherent limitations. The main one is the dependence on postmortem studies, which, by nature, work with small, convenience samples, often from brain banks with selection biases. Confounding variables such as age, cause of death, postmortem time until tissue fixation, and the presence of comorbidities (such as HIV infections, present in samples from classic studies) can influence neuronal morphology and nuclear volume, posing challenges for causal interpretation (RIVAROLA ESPINOZA, 2008), as shown in Table 5.

Another significant limitation is the difficulty in accurately and retrospectively categorizing the gender identity and sexual orientation of donors in postmortem studies, which often depends on incomplete medical records or information from third parties. The absence of longitudinal studies with high-resolution neuroimaging capable of visualizing structures as small as INAH-3 in vivo is still a technological gap. Connectivity studies, such as those by Kranz et al. (2014) and Spies et al. (2016) in Table 2, although innovative and , also face challenges of reproducibility and direct correlation

with the activity of specific hypothalamic nuclei.

CONCLUSION

This integrative review demonstrates that the scientific evidence accumulated over the last two and a half decades points to a central role for the Interstitial Nucleus of the Hypothalamus III (INAH-3) in the neurobiology of gender identity. Based on a critical analysis of the 22 studies included, it was possible to verify that INAH-3 is a robust marker of sexual dimorphism, with greater volume and number of neurons in cisgender men, a finding replicated by methodologically rigorous studies such as those by Byne et al. (2000, 2001), establishing the fundamental basis for investigations into individual variations in the sphere of gender identity.

It was also evident that gender identity has a structural correlate in INAH-3, with a complete reversal of the pattern of this nucleus in trans women (MtF) to the typical morphology of cisgender women, as demonstrated by Garcia-Falgueras and Swaab (2008), the most compelling evidence that gender identity is anchored in the deep neuronal organization of the hypothalamus, established early in development. Corroborating this interpretation, the differences observed are not explained by circulating hormones in adulthood, since structural (KRANZ et al., 2014) and functional (SPIES et al., 2016) neuroimaging studies demonstrate that the neural signatures associated with gender identity precede hormonal interventions, supporting the hypothesis of a cerebral organization of prenatal or perinatal origin.

Another key point is that the INAH-3 does not act in isolation, but is part of a complex and multifactorial neural network. Animal models investigating the sagittal nucleus of the hypothalamus (SGN), such as the works of Mori et al. (2009), Matsuda et al. (2017), and Balabanov et al. (2018), together with genetic and epigenetic studies (JAIN; RANA, 2021; ALAGHA et al., 2025; SARI et al., 2024), position INAH-3 as a central node influenced by polygenic architecture, epigenetic mechanisms, and hormones, integrating with higher-order cortical networks responsible for processing emotions and social cognitions.

The interpretation of these findings necessarily requires an ethical and social perspective. The consensus in contemporary literature points to the depathologization of gender diversity (BACK et al., 2019), emphasizing that the psychological distress observed in sexual and gender minorities (is intrinsically linked to stigma and minority stress (BHUGRA et al., 2022), rather than to identity itself. Translating this knowledge into clinical practice, professional training (SANTANA et al., 2021; SANTOS et al., 2024), and public policy is an ongoing challenge.

However, significant gaps remain. The reliance on postmortem studies, small sample sizes, and the difficulty of controlling for confounding variables remain methodological challenges. The following are recommended as future directions: the development of in vivo neuroimaging techniques with sufficient resolution to analyze INAH-3 in larger samples and longitudinally; the integration of neuroimaging data with genomic and epigenetic profiles; and the promotion of research addressing intersectionality, including often-neglected populations such

as the elderly LGBTQIAPN+ population (ARAÚJO et al., 2022).

Understanding INAH-3 does not imply biological determinism, but rather recognizing the complexity of the human experience. Science, in elucidating these mechanisms, must do so with ethical rigor and social commitment, contributing to the promotion of comprehensive health, respect for diversity, and the guarantee of fundamental human rights for all people, regardless of their gender identity.

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