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PERSPECTIVE

Perspective on equitable translational studies and clinical support for an unbiased inclusion of the LGBTQIA2S+ community

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Research regarding the mental health of the Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual, 2 Spirit (LGBTQIA2S+) community has been historically biased by individual and structural homophobia, biphobia, and transphobia, resulting in research that does not represent the best quality science. Furthermore, much of this research does not serve the best interests or priorities of LGBTQIA2S+ communities, despite significant mental health disparities and great need for quality mental health research and treatments in these populations. Here, we will highlight how bias has resulted in missed opportunities for advancing understanding of mental health within LGBTQIA2S+ communities. We cite up-to-date research on mental health disparities facing the LGBTQIA2S+ community and targeted treatment strategies, as well as guidance from health care professionals. Importantly, research is discussed from both preclinical and clinical perspectives, providing common language and research priorities from a translational perspective. Given the rising tide of anti-transgender sentiment among certain political factions, we further emphasize and discuss the impact of historical and present day ciscentrism and structural transphobia in transgender mental health research, from both clinical and translational perspectives, with suggestions for future directions to improve the quality of this field. Finally, we address current best practices for treatment of mental health issues in this community. This approach provides an opportunity to dispel myths regarding the LGBTQIA2S+ community as well as inform the scientific community of best practices to work with this community in an equitable manner. Thus, our approach ties preclinical and clinical research within the LGBTQIA2S+ community.

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INTRODUCTION

Science and medicine have a history of pathologizing the Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual, 2 Spirit (LGBTQIA2S+) community (definitions in Box 1). It was not until 1974 that same-sex attraction was removed from the Diagnostic and Statistical Manual of Mental Disorders (DSM), yet distress over same-sex attraction remained until 2013 [1, 2]. Research on the health of the LGBTQIA2S+ community has been biased by individual and structural homophobia, biphobia, and transphobia, resulting in research that fails to represent the best science. Here, we amplify the call from the community to de-pathologize these identities within science, particularly neuroscience and psychiatry. Furthermore, we describe the need for precise reporting of demographic data in health-related research, provide treatment directions, and convey such information to the public for both knowledge and policy decision-making.

Numerous examples exist of recently published studies pathologizing the LGBTQIA2S+ community; *even calling for eugenic practices to reduce our number - modifying the neural circuits of transgender, non-binary, and/or gender diverse (TNG) people to eliminate their transness*. We will not cite these papers. One retracted example is a review article from 2021 that compared altered neurotransmitter levels in LGBTQIA2S+ people vs. heterosexuals, to alterations in people with psychiatric conditions, arguing that LGBTQIA2S+ identity is innately pathological. The impact of minority stress on the LGBTQIA2S+ people was only briefly mentioned, despite well-established links between stress and psychiatric illness. The authors discussed the role of neurotransmitters in rodent partner preference, comparing to human sexual orientation. They manipulated graphs from another study, mislabeling axes to make it appear that drug treatment can ‘change’ an animal’s ‘sexual preference’ (male

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Box 1. Glossary of terms comprising the LGBTQIA2S+ community (adapted from Moreira et al. 2022)

Lesbian: A term used to describe women/girls who are attracted to women/girls: applies for cisgender and transgender women. Often referred to as homosexual, although this term is no longer used by the majority of women with same-gender attractions.
Gay: A term used to describe men/boys who are attracted to men/boys: applies for cisgender and transgender men. Often used and embraced by people with other gender identities to describe their same-gender attractions and relationships. Often referred to as homosexual, although this term is no longer used by the majority of people with same-gender attractions.
Bisexual: People who experience sexual, romantic, physical, or spiritual attraction to people of their same gender and toward another gender.
Transgender (male): Someone who identifies as male but was assigned female sex at birth.
Transgender (female): Someone who identifies as female but was assigned male sex at birth.
Queer: Historically a derogatory term used against LGBTQIA2S+ people, it has been reclaimed by these communities. Queer is often used to represent all individuals who identify outside of other categories of sexual and gender identity. Queer may also be used by individuals who feel as though other sexual or gender identity labels do not adequately describe their experience.
Intersex: Individuals who were born with any of several sex characteristics, which can include chromosomes, gonads, or genitals that according to the Office of the United Nations High Commissioner for Human Rights, “do not fit typical binary notions of male or female bodies.”
Asexual: People who experience little to no sexual attraction toward another individual, regardless of gender identity or sexual orientation.
2Spirit: “Two spirit” refers to an indigenous person, typically from North America, who identifies with a diverse range of sexualities and/or gender identities/expressions or spiritual identity and may encompass same-sex attraction and a wide variety of gender variance.
TNG: Transgender, non-binary, and/or gender diverse
GAHT: Gender Affirming Hormone Therapy - approved healthcare demonstrated to improve mood and reduce suicide rates

mounting behavior). *Such manipulations and misrepresentations are highly problematic.* Additionally, the trans community has been used as a ‘model’, or ‘natural experiment’ for hormone activity in the context of behavior and physiology, e.g., ‘inducing gender dysphoria’ in TNG people in the scanner to determine neural correlates. While it is important to be aware of the mistakes of the past, our commentary will focus on looking ahead to best experimental practices for basic and clinical science that can address the needs of the LGBTQIA2S+ community, starting with guidance on best clinical practices for this diverse community with specific mental health needs.

CLINICAL APPROACHES

Practical steps exist that can improve the mental health and quality of life for LGBTQIA2S+ people. The relationship between psychiatry and the community is fraught e.g., many TNG people require a diagnosis to access medical transition services with ICD-10 still using the term “gender identity disorder” for insurance billing. The APA replaced “gender identity disorder” with “gender dysphoria” for DSM-V (2013), paralleling changes made to homosexuality diagnoses (1970s/80 s). The terminology of disease and disorder highlights how LGBTQIA2S+ people have been harmed by the healthcare system, influencing access to gender-affirming hormone therapy (GAHT) and other TNG healthcare needs. Many studies documented discriminatory, even violent, treatment of LGBTQIA2S+ people seeking health care [3]. Even well-meaning providers often lack knowledge of appropriate care. These diagnostic issues are compounded by the now well-documented prevalence of discriminatory treatment of racial minority groups by the mental health field [4], with LGBTQIA2S+ people of color experiencing more deterrents to quality mental health care.

Members of the community are at increased risk for mental health struggles, including depression, anxiety, PTSD, substance use, and suicide [5]. Increased risk arise from factors including discrimination, marginalization, bullying, and loneliness. Unlike others, sexual and gender minorities are often stigmatized by their own families of origin, with long-term negative effects including underinsurance and housing instability [5]. Delineating the impact

of these stressors remain vital in working with this community and coordinating preclinical research (see below). These factors, plus negative prior healthcare experiences, impact clinic attendance, compounding difficulties faced by LGBTQIA2S+ people.

Providers hoping to support LGBTQIA2S+ people also face challenges, e.g., sufficient training [6], and avoiding/ignoring topics not understood. Some clinicians fear committing micro-aggressions, offending patients, or being out-of-date. Providers may refer patients to specialists, leading to a bimodal distribution in which providers see either few or exclusively LGBTQIA2S+ patients. Providers may have implicit or even explicit prejudice against sexual and gender minorities, compounding challenges faced by those seeking help. Finally, there is a growing movement from the political right using violent threats to intimidate and terrorize healthcare providers serving this community, particularly trans-youth providers.

Challenges are common, but steps can be taken to help LGBTQIA2S+ people lead healthy, joyful lives [7]. Clinicians should mirror patients’ language about their identities, relationships, pronouns, and bodies. Any misstep, briefly apologize and move on. Rather than assuming what a word or phrase might mean, take a curious stance, asking open-ended, clarifying questions (see Box 2). Validate the unique strengths of LGBTQIA2S+ people and affirm healthy or rewarding expressions of sexuality/gender. Identifying and restructuring any cognitions that may arise from minority stress, e.g., belief of personal failure, inferiority, or expectation of rejection (the latter is a constant experience within the community and not a distortion as it accurately predicts future experiences). Finally, as with all patients, it is vital to facilitate emotional awareness, regulation, and acceptance.

Clinics and research facilities are also important. Front-desk staff should avoid using gendered words/pronouns with new patients/participants. Gender-neutral bathrooms should be available. Protocols should exist to share names/pronouns, address mail, and leave phone messages for future contact. Easily accessible lists should be made of local and online LGBTQIA2S+ resources. Charts should lead with names and pronouns the patients themselves use. Finally, notes and auto-

Box 2. Inclusive questions to consider using during a clinical interview

- I use ___ pronouns, what pronouns do you use?
- What are the identities that feel the most salient or important for you?
- Who do you feel sexually or romantically attracted to?
- When you say (insert gender or sexual identity), what does that mean to you?
- Does your gender/sexual identity contribute to stress or anxiety in your life?
- Who's important in your life?
- If you need help, who are the people you can rely on?
- What do you love about yourself?
- As a (Black Queer) person, how do you experience this institution?

populated text should be gender-affirming. Such steps can destigmatize, minimize stress, and increase access to quality mental health care for all.

GENDER-AFFIRMING CARE FOR YOUTH

We have seen an onslaught of transphobic attacks on research and gender-affirming medical care presently available to TNG youth. Verbal threats against staff of pediatric gender clinics (2022), warranted increased police security for such university-based programs (<https://www.wcvb.com/article/boston-childrens-hospital-transgender-care-harassment/40924239>). A four-site NIH-funded research on GAHT was investigated for 'suppressing data not supportive of GAHT' – patently not true – while calls for more evidence-based studies of pediatric gender care were made and referred to as 'vital!' How can such research be conducted while under attack and meet the needs of trans youth, while being accused of child abuse?

The new paradigm of gender development articulates that gender variations are not psychiatric disorders and do not warrant treatment to "fix"/discourage gender expansive expressions/identities. Rather, children demonstrate multiple pathways to healthy gender consolidation, interweaving biology, socialization, and cultural context as they traverse from infancy to adulthood. There are increased number of adolescents seeking gender care worldwide, e.g., Tavistock and Portman group from the UK's National Health Service reported >2500 referrals (2021), up from 137 (2011). Researchers and social commentators, asserted that this increase [they describe as "rapid onset gender dysphoria" (ROGD)], is a form of contagion due to social influencers and activist-providers promoting a 'transgender agenda'. This work was conducted from a biased sample i.e., recruited from online forums for parents unsupportive of their child's identity. This 'sudden' disclosure of transgender identity is more likely because youths knew they were transgender and did not disclose because they (rightly), suspected poor support. A simpler explanation comes from the experience of left-handed people. Actuarial data reveal a jump in left-handed people from 2–10% (1900–1950), remaining consistent at ~10% to this day [8, 9]. Sudden onset of left-handedness was not a contagion, but likely arose from removing the taboo against left-handedness, who prohibited from expressing left-handedness, were forced to use their right. *Lifting left-handed prejudice enabled more left-handed people to live an authentic left-handed life.* Likewise, lifting biases against gender diversity enables youth to explore and articulate their authentic gender selves, increasing numbers seeking GAHT. The fact that many cisgender people express concern about numbers of TNG people is telling. The notion that, as a society, we should limit the

number of people allowed access to medical transition belies claims that handwringing regarding TNG youth is not rooted in bigotry.

No major professional association has validated ROGD. Such pseudo-scientific claims contribute to transphobic rhetoric and action, e.g., protests at facilities providing TNG care. Researchers continue to study and publish peer-reviewed reports on GAHT that help children, practitioners will continue to provide such care. GAHT reduces odds of depression and suicidality, representing a vital health care intervention [10]. High rates of satisfaction among receiving such care [11], support its continued practice to help the small Ts in this community.

PRECLINICAL RESEARCH-SEX DIFFERENCES

How can researchers conduct preclinical work that benefits LGBTQIA2S + communities? Rodent models enable the study of LGBTQIA2S + health, if used with due consideration of translational applicability and to societal issues faced (not reproducible in rodents). While such limitations need to be considered generally, interpretation of rodent behavioral data presents a particular challenge for questions related to gender identity/sexual orientation given political standpoints [12], writing laws for political expediency hurting LGBTQIA2S + youth. Too often researchers still confuse socially constructed concepts of 'gender' with 'sex', only the latter is observable in rodents based on anogenital distance differences, gonads, or XX or XY chromosomes. These concepts are often rooted in bioessentialism and phrases like "biological sex" can be anti-trans dog-whistles.

While research study design include both sexes, rodent experimental outcomes usually do not show a binary profile when comparing females and males. Sex differences in biological and behavioral measures can be observed, but there are distribution variances overlap. Female rodents are not necessarily more variable than males [13], a premise precluding use of females in research for decades. Overlapping variance may suggest that rodent behavior may not be sexually dimorphic and consideration of female and male data as a continuum in rodent studies.

We urge caution when attempting to study the neurobiological mechanisms underlying gender identity/sexual orientation. *One crucial consideration for this research lies in the challenge of finding relevant behavioral correlates of human sexual preference in rodents.* Studies have assessed effects of hormones or neurotransmitters on mounting behavior to evaluate sexual preference, but this behavior is also a sign of aggression/dominance in rodents - not applicable to human sexual orientation. Furthermore, it is unclear how knowing the biological basis of sexual orientation/gender

Box 3. Suggestions of an off-ramp for future researchers and clinicians to lead to better mental health for the LGBTQIA2S+ community, their families, and all

1. Use inclusive language in the clinic (see Box 1).
2. Use of inclusive language in research focusing on the variables themselves rather than expressing variables in simple binary terms (e.g., menstruating people), would improve reproducibility across studies and reinforce that sex is simply a context-dependent summary.
3. Recognition that new paradigm of gender development articulates that gender variations are not psychiatric disorders and do not warrant treatment to “fix” or discourage gender expansive expressions/identities. Rather, children demonstrate multiple pathways to healthy gender consolidation, interweaving biology, socialization, and cultural context as they traverse from infancy to adulthood.
4. Major institutions to put out a statement making clear their recognition on the harms of the past and the need to move toward a better future, limiting opportunities for hate groups targeting the LGBTQIA2S+ community, e.g., recognizing the harm of same-sex conversion therapy, making it illegal (as done in California, the UK, etc.).
5. Enabling inclusivity at the level of choice where scientists can gather to share ideas (conference venues). Avoid locations with anti-LGBTQIA2S+ laws (e.g., from death penalty, Uganda; imprisonment, Qatar; to punishment for using chosen gendered bathroom, Arizona).
6. Avoidance for use of mounting behavior as a surrogate for sexual preference in rodents.
7. Preclinical longitudinal research on GAHT effects on: 1) gene expression in the brain; 2) neural processes involved in affective-relevant behaviors; 3) neural networks controlling social behavior; 4) cognitive processes; and 5) neurological control of metabolism and physiology

identity research would improve LGBTQIA2S + health. Research should be guided by the need to address health challenges disproportionately affecting this community. Thus, rodent research aimed at better treating/preventing stress effects and on long-lasting behavioral outcomes will benefit LGBTQIA2S + communities. Other species exist for which same-sex preferences may be clearer (e.g., non-human primates), but such laboratory-based research opportunities remain limited. Either way, the choice of any model to improve LGBTQIA2S + health should be guided by the specific needs of the community. Improving treatments or preventions to mitigate the impact of minority stress on mental health should certainly take precedence over understanding the biological basis underlying LGBTQIA2S + identity.

PRECLINICAL RESEARCH-GAHT

Translational research historically failed to acknowledge TNG or intersex people. The first animal model of GAHT use was recent [14]—one year after the U.S. National Institute of Health mandated use of females (in addition to males), in research. No regulations yet require gender expansive individuals be included. Randomized controlled trials on GAHT cannot be ethically conducted because GAHT is already established as the standard-of-care improving mental health outcomes [10, 15]. This lack of research enables the pathologization of TNG people, promoting discriminatory policies (Miyagi et al 2021), including restricting GAHT access [16].

Animal models of GAHT enable genetic manipulation and precise neuronal/molecular recordings impossible in humans. Thus, researchers can address deficits in our knowledge of GAHT effects specifically: (1) gene expression in the brain; (2) neural processes involved in affective-relevant behaviors; (3) neural networks controlling social behavior; (4) cognitive processes; and (5) neurological control of metabolism and physiology [17]. Each process requires careful longitudinal monitoring coupled with community-based knowledge to ensure that translational research addresses the needs of the TNG community. Additionally, such research should be mindful of the language used to describe patterns of GAHT effects, avoiding pathologizing language (e.g., “impair”/“deficit”), instead utilizing “reduce”/“increase”, when describing outcomes.

It is important to state that in expanding our understanding of the effects of hormonal and developmental state on TNG identity, researchers do not contribute to biologically essentialist notions of gender and sex. Setting arbitrary biological parameters for TNG identities would serve as an additional barrier to accessing healthcare. Such stressors coupled with increased rejection sensitivity would lead to healthcare avoidance, devastating mental health [18–21]. Translational research should also answer the questions raised above at important developmental stages [17], to inform the long-term impact on TNG-relevant physiological outcomes.

Most biomedical and sociocultural discussions of GAHT outcomes focus on physical characteristics, not neurological impacts. Avenues for future research include, investigating the impact of gonadal hormonal milieu on psychiatric medication efficacy, response to rejection and ostracization, cognition during chronic stress, and metabolism throughout life. Utilizing translational research approaches to help the TNG community vs. using that community-are urgently needed for their mental health.

DISCUSSION

The long-history of stigmatizing the LGBTQIA2S + community (from those providing care, the public, families, to leading neuroscientists and psychiatrists), has increased their susceptibility to psychiatric illness. The actions of the political right and other groups, attacking LGBTQIA2S + people, organizations, researchers, and clinicians, should be of increasing concern. We warn neuroscience and psychiatry against the use of their work and express a call-to-action in support of our LGBTQIA2S + community. Such stigmatization and negative (including traumatic), experiences drive stress responses, negatively impacting mental health [5]. Previously, this stress feedback was not well-handled in the clinic, given stigmatization, lack-of-knowledge, and poor training. Thus, while we acknowledge stress contributions to the development of psychiatric conditions, psychiatry and neuroscience have long-contributed to the higher odds-ratio of occurrence within the LGBTQIA2 + community. Going beyond recrimination, however, we show here that researchers and clinicians can provide an off-ramp to better mental health for all (Box 3).

We know that GAHT lowers odds of depression and suicidality [10], with high rates of satisfaction [11], thus is a vital health care intervention. Research understanding the impact of GAHT are still required. GAHT impact on brain gene expression, neural networks involved in affective, social-, and cognitive-relevant behaviors, plus metabolism and physiology (at all developmental stages), can be determined preclinically—studies unfathomable in humans. Such research recognizes that caution should be taken when attempting to study the neurobiological mechanisms underlying gender identity/sexual orientation, as relevant behavioral correlates of human sexual preference remain unclear. Overlapping biological and behavioral variance seen between male and female rodents suggest viewing these data as a continuum. Importantly, all research should be guided by the need to address health challenges disproportionately affecting this community, including minimizing stress impacts in future studies.

Ultimately, with increased TNG youth requiring GAHT, scientists should be able to help using approved techniques that reduce depression and suicidal ideation rates without violent or political threats. While generating data on such care, the scientific field should be wary of it being used to create scientific-sounding issues as providing cover for anti-trans dog whistles [e.g., ROGD [22]]. *TNG is not an illness – there is no ‘contagion’*. Increased visibility and awareness give people the language for self-expression. Recognizing people as they are is an important step toward improving mental health in the community.

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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