Review

Biological Psychiatry: CNNI

Refining Research and Representation of Sexual and Gender Diversity in Neuroscience

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ABSTRACT

There are opportunities to improve neuroscience that include lesbian, gay, bisexual, and transgender (LGBT) people. In this review, we briefly describe how the history of LGBT people in psychiatry has influenced neuroimaging approaches; how these attitudes have shifted over time; and what we can do to ensure that our future work is rigorous, ethical, and in service of the LGBT community. We suggest ways to refine neuroimaging methodologies to improve our understanding of marginalization and stigma while shifting away from research that focuses solely on the "etiology" or origins of LGBT identities. We also offer suggestions for conducting representative research that is LGBT-inclusive, regardless of the population of interest.

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Lesbian, gay, bisexual, and transgender (LGBT) communities experience social marginalization and stigma that contribute to elevated rates of depression, anxiety, and substance abuse, to name a few (1). There is increasing recognition of the impact of minority stress and stigma on the brain and body as well as contributions of marginalization to mental health disparities. Historically, biological psychiatry and neuroscience have unfortunately often engaged in practices that pathologized LGBT identities. In this article, we provide an overview of the history of LGBT people and psychiatry, how this history has influenced the way research is conducted in these populations, and what we can do to progress research in this area in partnership with LGBT communities.

WHERE HAVE WE BEEN?

Homosexuality was included in the DSM by the American Psychiatric Association until 1973. This diagnosis persisted in DSM-III as "ego dystonic homosexuality." Likewise, "transsexualism" first appeared in 1980 in DSM-III, was changed to "gender identity disorder" in DSM-IV, and is now referred to as "gender dysphoria" in DSM-5-TR (2–4). These shifts in terminology acknowledge stress caused by internalized homophobia and/or gender incongruence rather than the pathologizing of identities themselves; however, this argument is widely contested, as inclusion of ego dystonic homosexuality still legitimized attempts at conversion therapy, and the gender dysphoria diagnosis continues to undermine patient-centered approaches to medical decision making (2,5).

People studying the "etiology" of LGBT identities have sometimes argued that fixating on a biological basis reduces bias. However, this is not consistent with the literature of bias (6–8), nor is it consistent with the way many scientists frame and interpret findings (9). Indeed, this argument ignores the use of innate biological difference to reinforce and naturalize, for instance, racist and ableist hierarchies (10–13). Moreover, the notion that sexual orientation has a biological basis first arose in the context of attempts to "cure" gay men, gay women, and gender diverse people as much as it was used to support civil rights (14).

Biological determinism can also be tied to notions of dimorphisms and binary sex that are outdated. This includes early ideas that gay men and women have the body of one sex and the soul/mind of another (15). This idea persists in modern neuroimaging studies that claim that the brains of gay people are "sex reversed" and less sexually differentiated than the brains of heterosexuals (16,17). Historically, the concept of binary sex has roots with the American and European eugenics movements of the early 20th century. The concept was used to justify racial hierarchies by arguing that biological differences between men and women were most prominent among White people and less pronounced among people of color, particularly Black people (18,19). Even today, the construction of terms such as sexual orientation, gender, and sex by medicine is ever evolving, not neutral, and can carry heavy baggage from their history. In the absence of a historical mindset, scientists can easily recapitulate and reinforce harmful ideas about LGBT people, regardless of their intentions.

To date, most of the LGBT neuroimaging literature focuses on the etiology of identities (20). Studies generally compare cisgender and transgender groups or cisgender heterosexual and cisgender gay or lesbian people (16,21–25). This approach underscores a framework that assumes cisgender heterosexuality as the default, and variation in sexual orientation or gender identity as aberrant. For example, most neuroimaging studies that use group comparisons include extensive psychosocial evaluations of sexual orientation and gender identity in their LGBT groups, but not in their "control" groups. However, all people have sexual orientations and gender identities, including those who do not identify as LGBT. Other studies use

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erotic stimuli to argue that the pattern of activation to same-sex erotic stimuli in gay men and women is similar to the pattern of activation to opposite-sex stimuli in heterosexuals (24–29). The preponderance of studies focused on erotic stimuli overall suggests an unnecessary preoccupation with the identification of biological markers of arousal to validate the experiences of LGBT people. There are also methodological concerns with the LGBT neuroimaging literature, including small sample sizes and lack of appropriate statistical correction. In addition, there are problems with nonrepresentative samples and choice of comparison groups [for review, see Levin *et al.* (30)].

Although often unintentional, group differences can be misinterpreted in the absence of strong theoretical models. A recent review of the neuroimaging literature of sexual orientation found only one article that examined minority stress. In this review, the authors argue that because researchers have focused on the etiology of sexual orientation at the expense of the effects of social marginalization on the brain, differences in default mode and emotional processing networks, well-established neural correlates of psychological distress in the psychiatric neuroimaging literature, are attributed to sexual orientation. This field of research moves forward despite no integration of theoretical models or mechanism for a relationship between emotional regulation or default mode network connectivity and sexual behavior (20). In other fields such as psychology and public health, rich theoretical models on sexual and gender minority stress have been developed for decades (31–34). Yet, these theoretical models are not adequately integrated in neuroimaging studies from hypotheses to interpretations.

Similarly, in the case of the transgender neuroimaging literature, some studies attribute differences in somatomotor cortex in transgender people to cross-gender identification, arguing that differences in this brain region are the cause of transgender identity (35,36). These claims highlight the lack of a priori model building in this literature. For example, why would differences in somatomotor cortex cause someone to be a man or a woman, when such findings are not consistent with the cisgender sex differences literature? A more plausible explanation is that differences in somatomotor cortex may be due to disconnection with one's body learned as a coping mechanism for gender dysphoria (37). Indeed, there is evidence that transgender people show reduced responsiveness in somatomotor cortex to tactile stimulation of body parts associated with gender dysphoria, but not other body parts, relative to cisgender controls (37).

Another example of harm done by the lack of a priori model building is the tendency to conflate the terms transgender and gender dysphoria. This elision creates problems when studies purport to study gender dysphoria, but assess only transgender identity. This is exemplified by a recently retracted article that argued for the use of neuromodulatory interventions as a reparative therapy because of the literature attributing somatomotor cortex to transgender identity (38). It is important to emphasize that reparative therapy practices are unequivocally harmful and ineffective (39).

In another relevant example, a recent genetic study of transgender people contended a causal link between the initiation of hormone therapy and alterations in DNA methylation over the first year of transition (40). However, such studies should also consider the psychosocial shifts that occur during this period of transitioning and the potential for effects of the changing social environment. In particular, increases in psychosocial stressors on biological variables of interest should be considered. Also, positive health and wellness related to gender affirmation should be considered beyond focusing solely on negative effects. Identification of group differences without consideration of the social contexts of LGBT people has the potential to reinforce ideas about LGBT people as abnormal, deviant, or disordered. Lack of a priori model building can therefore result in assumptions of causality that create the potential for harm.

We encourage thoughtful theory building as a way of mitigating the concerns outlined above (41–43). Such theory building will necessarily require that researchers engage in empathic perspective taking when studying LGBT people. What are the social developmental experiences of LGBT youths, and how do they impact biological stress systems? How does parental and peer rejection influence the development of neural networks associated with social and emotional processing? How might years of dissociation from one's body, practiced as a coping mechanism in the context of gender dysphoria and body dysmorphia, affect sensory cortices?

Given the astoundingly high rates of depression and anxiety disorders among LGBT populations, particularly LGBT youths (1), understanding the downstream effects of social rejection and bodily trauma on the developing brain could help us better understand the pathophysiology of mood and anxiety disorders. This could in turn contribute to the identification of novel intervention targets tailored to individuals whose symptoms may be the result of chronic developmental trauma, stress, and adversity. Although there has been relatively little work on factors associated with resilience among LGBT communities, there is some literature suggesting that community connectedness may be an important buffer to the long-term effects of stress and social rejection (44). Work among LGBT youths has found that parental acceptance is also a critical factor associated with resilience to depression and anxiety (45,46). These social and interpersonal factors have yet to be thoroughly investigated in the neuroimaging and biological psychiatry literature and are an open area for future study.

LOOKING AHEAD: HOW TO DO THIS WORK WELL

Participant Recruitment

Studying vulnerable populations requires careful consideration regarding recruitment. For example, LGBT youths could be outed to their caregivers via consent forms, and additional care should be taken to ensure that consent forms and recruitment materials are thoughtfully worded (47). Furthermore, most studies of LGBT people are overwhelmingly White, even though people of color are overrepresented in LGBT communities (48). In the case of transgender people, recruitment from gender clinics results in nonrepresentative samples, which tend to be more affluent, White, and binary identified. This representation is also due to the ways in which racism, transphobia, and poverty intersect to impact access to health care (49–51).

In addition, many LGBT neuroimaging studies exclude for psychiatric disorders (35,52–64). This exclusion again results in nonrepresentative samples (65). Transgender neuroimaging studies also typically use the psychiatric screening performed during evaluation for transition-related services to determine participant eligibility (52,55,57,58,63). Until very recently, the World Professional Association of Transgender Health Standards of Care stated that mental health concerns must be "reasonably well-controlled" before initiation of hormone therapy (66). Consequently, transgender people may not be forthright about their mental health during this evaluation process (51,67–69).

There are a number of additional ethical considerations in recruitment of transgender people in particular. For example, because of gatekeeping of transition-related care (49), we should ensure that transgender people understand that their participation in research will not affect access to health care. Concerns about consent can be addressed in this population by recruiting from the community, not only from gender clinics. If recruitment is indeed conducted from gender clinics, there should be a clear separation of clinical care and recruitment for research studies (47). Finally, transgender people are a relatively small population that is over-researched in psychiatry. Bioethics scholars are citing research fatigue as a major ethical concern (70). Research fatigue is a phenomenon distinct from participant burden in human participants research. Briefly, research fatigue describes a process by which members of small, vulnerable minority communities become exhausted by repeated requests to participate in research with little to no chance of benefit to their community. This results in selection bias and negatively impacts the quality of our science as well as relationships between marginalized communities and researchers (71). These concerns can be mitigated using community-based participatory research approaches (72).

Data Collection

Demographic data collection rarely includes sexual orientation or asks about gender and sex. A 2-step question that asks about gender identity followed by sex assigned at birth allows for more precise data collection (73). The use of sex, gender, and sexual orientation as binary or categorical variables is also imprecise. There is little consideration of the component parts of sex and gender as continuums. These constructs can be disassembled, and their components can be measured as continuous variables (74,75). For example, measuring testosterone and estrogen provides a continuous measure of sex hormones (76). This is consistent with work on brain mosaics that go beyond sex as a binary variable in neuroscience (77–80).

When we consider sex as a biological variable, we should first reflect on what component of sex we hypothesize will be relevant to our outcomes of interest. Sex is a complex construct that includes endocrine status and genetic makeup as well as a great deal of phenotypic variation. If we are interested in gender, we must consider gender nonconformity, stress, and social marginalization. We must also differentiate between sex and gender. This is a practice that all researchers should engage in, regardless of the population of interest. The most appropriate way to collect data about sex, gender, and sexual orientation will vary considerably from study to study and from discipline to subdiscipline. However, we urge researchers to reconsider the use of a single binary variable to encompass both sex and gender, as is currently the dominant practice. For researchers interested in assessing their approaches to data collection regarding sex and gender, we recommend the Gender and Sex in Methods and Measurement Toolkit (81).

We should also examine our diagnostic and assessment measures and behavioral/functional magnetic resonance imaging (fMRI) paradigms for ciscentrism and heterosexism. For example, instruments normed by gender may not be valid in transgender or gender nonconforming populations. We also should implement measures of experienced discrimination to understand its consequences (82–85). We may also consider differing interpretations of fMRI task stimuli. There is evidence that in-group versus out-group status is associated with differences in brain response to fMRI task stimuli (86). Do LGBT people assume that standardized face stimuli share their identities, or do they interpret these stimuli as representatives of the dominant group? Furthermore, for many face processing tasks, we ask participants to make a gender designation via button press to ensure they stay engaged. Transgender people may experience this task with more discomfort or emotional distress than cisgender people. The measures and tools we use and our interpretation of them can be biased. Therefore, we must carefully examine our own prejudices, particularly in the context of symptom or diagnostic assessment to avoid stigmatizing research participants.

Data Analysis

All people have sexual orientations and gender identities, expressions, and modalities. If we measure these variables as continuous constructs as opposed to categorial variables, we avoid the problem of being underpowered to detect effects or interactions. It is also important to consider comparison groups. A representative sample of LGBT people will have high rates of psychological distress. It may be most appropriate in some instances to include a comparison sample that is matched for symptom severity to avoid potential confounds (87). In other cases, within-group comparisons can be made without a cisgender or heterosexual control group. For example, transmasculine people who experience greater stigma or live in less progressive places, respectively, show higher diurnal cortisol (88) and allostatic load (89) compared with transmasculine people with more positive lived experiences. Another common oversight in studies of transgender people is the use of a cisgender sample matched for sex assigned at birth, without consideration of gender identity. This results in flawed data interpretation, whereby observed differences are attributed to transgender identity, when findings may instead simply be gender differences that are also present between cisgender men and women.

Dissemination of Findings

Given the recent wave of legislation designed to restrict access of transgender people to health care and public space, there is much public policy interest in LGBT research. Indeed, politicians in the United States have misrepresented research related to LGBT identity or rhetorically weaponized debunked

studies to restrict access to health care for transgender youths (90). We must be prepared to discuss this in an accessible manner with the public. It is not possible to depoliticize our work, and we should be aware of the political climate, the history of the field, and the possible implications of our findings for marginalized people. Homophobia and transphobia are pervasive social problems, and scientists are not exempt from these biases. Indeed, neuropsychiatry has contributed to the prejudices and disparities we see in LGBT communities. It is therefore our duty to address these harms in collaboration with community members.

CONCLUSIONS AND FUTURE DIRECTIONS

The types of research questions we ask reflect our values and priorities. At this moment, we are seeing a pivot from a focus on etiology to a recognition of the effects of minority stress on the brain and on mental health (91). For example, an fMRI study of social rejection found a more persistent medial prefrontal cortex blood oxygen level–dependent response to ostracism in transgender people in comparison to cisgender people (92). Others have identified differences in autonomic and hypothalamic-pituitary-adrenal axis function in sexual and gender minorities (93–101) as well as physiological functioning in individuals who are multiply minoritized owing to transphobia, sexism, homophobia, and/or racism (102,103). Such approaches are underpinned by a different theoretical orientation than studies that attribute group differences to innate biology. They also allow for consideration of intersectionality and developmental/psychosocial stressors.

Relatively little is known about the developmental effects of experienced homophobia/transphobia on attachment, biological stress systems, brain structure and function, and risk for psychiatric disorders. Work that describes the phenomenology of psychiatric symptoms in LGBT people or the relative efficacy of extant psychiatric interventions in LGBT communities has been scarce. Future work should examine factors associated with vulnerability and resilience to LGBT-specific stigma as well as the development and evaluation of novel interventions designed to improve the mental health of LGBT communities.

Community input must be integrated at every step of the research process (Figure 1). This includes collaborating with LGBT colleagues and peers, mentoring LGBT trainees, and creating compensated community advisory boards. Partnership with LGBT communities encourages recruitment and contributes to novel hypotheses or interpretations of findings. By partnering with LGBT communities, we can also ensure that our research adds to community knowledge, that we study phenomena that are of concern to the community, and that we interpret our findings within the appropriate social context.

Building relationships with communities takes time. There is often suspicion of psychiatry and biological sciences in many LGBT communities. This lack of trust is the consequence of a century of pathologizing of LGBT people by psychiatry, including the use of behavioral therapy to convert LGBT people (104), the ongoing exclusion of LGBT people from careers in science (105), and the close historical coupling of psychiatry and biological sciences with 19th and early 20th century eugenics movements in the United States and Europe (106–108). This lack of trust is compounded and perpetuated today by a tendency toward health equity tourism by researchers (109). Health equity tourism is a phenomenon in which researchers without prior commitment to or expertise in topics related to health equity engage in this work in an opportunistic or reactionary fashion, often resulting in harm to marginalized people (109,110). Even in the case of researchers with largely altruistic motivations, it is critical to remember that the study of health inequality is itself an area of expertise that requires training, education, and thoughtful collaboration with academic and community experts.

Academic research has long operated via an extractive model, whereby data are collected from marginalized communities and interpreted by the dominant group. Individuals

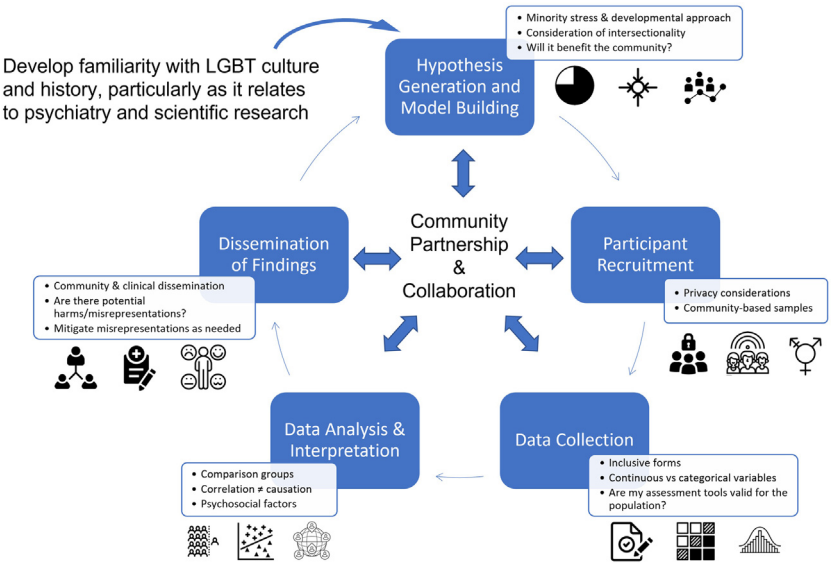

Figure 1. Strategies for research in partnership with lesbian, gay, bisexual, and transgender (LGBT) communities.

from those communities are often not seen as reliable sources of knowledge. Instead, in an example of epistemological injustice, members from the dominant group may be seen as objective, while community members are not (110). We must shift from this extractive model toward a partnership model that values lived experience and does not exclude community members from the process of knowledge production. In closing, it is imperative that we approach marginalized communities compassionately with humility and respect for their expertise and lived experiences.

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