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An Ethical Analysis of Performing Brain Studies on Transgender People

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The AIDs epidemic that began in 1981 led to a peak in equity and ethical concerns surrounding LGBTQ+ persons seeking medical treatment, concerns that continue to rage on in present day politics, hospitals, and research studies. The 1980s saw the birth of ACT UP and the rise of the LBGT rights movement, together revolutionizing the treatment of queer people and their access to medical care. The gay rights movement catalyzed a reevaluation of queer, gay, and transgender “diagnoses,” visible in the subsequent revisions made to the Diagnostic and Statistical Manual of Mental Disorders.¹ Growing curiosity and the scientific need to determine the etiology of queerness have led interested researchers to conduct dozens of brain studies which attempt to identify the neurophysiological origins of queerness, specifically targeting homosexual and transgender persons. Although limited, a great deal more of existing ethical literature addresses the implications of performing brain studies on homosexual individuals in contrast to those being performed on transgender persons. Ethical analyses of brain imaging research studies on transgender brains are scarce; consequently, much of the ethical literature that will be referenced draws from other queer and gay brain study analyses. The subject is simply not being addressed, despite a wealth of gross ethical concerns that are evident in published research studies, which is precisely why more evaluative ethical examinations *must* be conducted on the matter. In a minority population so prone to exploitation and mistreatment, it is *critical* that appropriate protections for study participants be established and enforced.

Within gender studies, *transgender* is an umbrella term that applies to individuals whose experienced gender -- also referred to as gender identity -- differs from their sex assigned at birth. This notion that born physical characteristics do not always align with gender identity is also known as gender incongruence (GI) or gender dysphoria (GD), which are used

¹ A comprehensive guide used by the American Psychiatric Association for the classification and diagnosis of mental disorders

interchangeably (Starcevic et al., 2020; Altinay & Anand, 2020; Ramirez et al., 2021). The majority of the brain studies that aim to identify the underlying neurobiological mechanisms of GI utilize structural MRIs, functional MRIs, and Diffusion Tensor Imaging (DTI) in vivo, although some research has been conducted using post mortem brains (Sorouri Khorashad et al., 2020; Mueller et al., 2021; Manzouri et al., 2017; Altinay & Anand, 2020). Structural MRIs allow for researchers to identify structural brain differences between transgender and cisgender participants (Mueller et al., 2021; Sorouri Khorashad et al., 2020; Starcevic et al., 2020). Some resting-state functional MRIs are used similarly (to contrast regional brain activity in trans- and cisgender participants) while task fMRIs measure brain activity in target areas after transgender participants are asked to think about their bodies and perception of their physical self (Manzouri & Savic, 2019; Manzouri et al., 2017). DTI is utilized in some brain imaging studies with transgender participants to examine fractional anisotropy, a measure of white matter tracts and neuronal connectivity (Altinay & Anand, 2020; Assaf & Pasternak, 2008; Kreukels & Guillamon, 2016).

The application of brain imaging studies on transgender people walks a very fine ethical line between simply identifying an underlying biological mechanism responsible for feelings of GI and misusing findings to develop a “treatment” or “cure” for gender dysphoria. Attempts to convert transgender people to think of themselves as their born gender or de-transition are prevalent in recent studies. In many instances, published research findings use outdated, pathologizing vocabulary that clings to binary confines, implies dysfunction, and passes moral judgment on participants within the study (further detail below). However necessary comparison may be for the etiological understanding of transgenderism, the enforced binary of trans- and cisgender subjects in these comparative studies rarely affirms gender identity.

There are various models resulting from hypotheses on social, biological, and neuroanatomical etiology of transgenderism, all of which rely on the maxim that sexual differentiation causes sexual dimorphism in the brain.² The sexual differentiation hypothesis is grounded in studies that evaluate whether the brains of people who experience GI more closely resemble their birth sex or their gender identity by comparing them to cisgender persons (Kreukels & Guillamon, 2016). It is hypothesized that changes in levels of sex hormones during prenatal development cause the genitals and body to develop towards one sex and the brain to develop towards another (Swaab & Garcia-Falgueras, 2009). Neurobiological models establish a link between atypical sexual differentiation as a result of sex hormone levels in utero and successive atypical development of brain structures associated with perception of one's own body (Uribe et al., 2020). Studies generally reflect greater cortical thickness as well as weakened structural and functional connectivity in the anterior cingulate-precuneus and right occipito-parietal cortex in transgender participants when compared to cisgender individuals (Manzouri & Savic, 2019). The anterior cingulate-precuneus and right occipito-parietal cortex are both brain regions critical in first-person body perception, self-oriented mental representations, and self reflection (Vogeley et al., 2004). Theoretically, these brain regions are pertinent in the etiology of transgenderism, as they influence perceived gender, and weakened functional connectivity may present as gender-related body dysphoria (Caselles, 2021).

However, neuroanatomical sexual differentiation has only been identified in rodents, and findings have not been explicitly tested in human studies. Instead the findings have merely been generalized and assumed to translate to human neuroanatomy. Rodent research established the sexual differentiation paradigm in which exposure to hormones -- including estradiol and

² Distinct morphological differences between the two sexes of a given species

testosterone -- activates sexually defining characteristics in the gonads and the brain early in development, subsequently masculinizing or feminizing affected brain structures (Fitch & Denenberg, 1998; Lenz et al. 2021). Because of the lack of evidence supporting an accurate application of rodent research findings to humans, some studies reject the theory that prenatal sex hormone levels contribute to the irregular development of structures associated with gendered body perception. Such research operates on the hypothesis that neuroanatomical differences exist in isolation from prenatal hormone influence (Manzouri et al., 2017; Manzouri & Savic, 2019). Others have theorized that there are heritable genetic components that lead to GD and transgenderism, including a polygenic model that considers the effects of genetics and environment as well as a model that addresses differing global CpG methylation profiles between cis- and transgender participants (Polderman et al., 2018; Ramirez et al., 2021). Alternative neuropsychobiological models agree with the sociocultural element introduced by the polygenic model but reject genetic factors. Instead, these neuropsychobiological models suggest a feedback loop between atypical neuroanatomy affecting body perception, behavior, and environment that is not considered by polygenic models (Altinay & Anand, 2020; Mohammadi & Khaleghi, 2018). This wholistic approach is the most widely accepted in neuroscience, despite contradictory evidence and severely limiting factors, such as study sample size and difficulties controlling for sexual orientation (Starcevic et al., 2020; Garcia-Falgueras & Swaab, 2008; Manzouri & Savic, 2019).

Many researchers blatantly disregard studies that refute neurobiological explanations which depend on sexual differentiation to explain gender identity. Consequentially, studies and results exist in a vacuum, excluding those who do not align with a binaried gender identity and exacerbating the oppression of gender nonconforming persons (Meuller et al., 2021). The issues

of binarized terminology are evident in ethical analyses addressing etiological brain studies involving homosexual men which have sustained and reinforced socially constructed biological sex labeling (McLaughlin, 2018). This is especially counterproductive as the studies' results fail to support a binary model, and instead expose a spectrum of sexual orientation. Previous research has been limited by the binary narrative both as it applies to sexuality and to gender identity. As has been discovered with regard to sexuality, gender identity also falls on a spectrum, evidenced by the existence of non-binary and gender nonconforming people. The binary restrictions for both cis- and transgender participants gives rise to misuse of pronouns and misgendering of transgender participants in published findings, which complicates analyses and interpretations of this research.

The labeling and terminological inaccuracies found within transgender brain studies exhibit the gross negligence of and disregard for social and political responsibilities to protect a vulnerable population on behalf of involved researchers, editors, review boards, and publishers (Caselles, 2018). Even more disturbing, this is not for lack of literature addressing the ethical considerations that should be acknowledged when undertaking research on transgender health. Numerous reviews layout guidelines that should be followed in future studies so as not to infringe on the autonomy of transgender participants and prevent the misuse of study findings (Dubois & Shattuck-Heidorn, 2021). One such article emphasizes unnecessary pathologizing terminology, suggesting that it passes moral judgement on research participants and can cause harm both as research is being conducted and at the time of publication (Adams et al., 2017). Ultimately, pathologizing vocabulary should be avoided as it obscures the objectivity of the research and furthers a narrative of dehumanization for non cisgender people. Vocabulary such as 'comorbid,' 'extreme,' and 'persistent' are also not appropriate terms when discussing

transgender people and GD, as they connote disorder and dysfunction. Gender identity brain studies published as recently as 2021 make use of the term “gender-identity disorder,” an outdated term that was replaced in the DSM-5 over eight years ago by “gender dysphoria” which acknowledges non-binary identities and aims to depathologize gender identity (Casellas, 2021). Nevertheless, contemporary brain studies continue to refer to GD as “comorbid” and “persistent,” while describing behaviors intended to affirm gender identity as “inappropriate,” “wrong,” and “improper... misunderstanding[s]” of biological, assigned sex (Mohammadi & Khaleghi, 2018, pp.137-141).

Although ethical study guidelines encourage IRB boards to reject brain studies focused on transgender people that include conversion, reorientation, or reparative therapy, there is no social or psychological research on the application of ethical research standards within transgender populations (Adams et al., 2017). This is a fundamental concern because of the extreme marginalization, oppression, and violence that transgender individuals still face. In the absence of ethical research standards specific to transgender research participants, no active practices or preventative measures have been designated to protect transgender people as a vulnerable population in neuroscience research. Without stringent safeguards in place, research studies that theorize on potential conversion treatments to “correct” gender incongruence *using transgender participants* can be conducted and published. This egregious ethical violation can be seen in a pathological research study by Mohammadi & Khaleghi conducted in 2018:

“Transgender individuals experience change in lifestyle, context of beliefs and concepts and, as a result, their culture and behaviors. Given the close relationship and interaction between culture, behavior and brain, the individual’s brain adapts itself to the new condition (culture) and concepts and starts to alter its function and structure... Thus, we believe that after a certain period of management, transgender individuals can be driven toward culturally contextualized behaviors via changing the specific cultural environment

and lifestyle and can be adapted to their original biological gender through trying to enjoy a natural sexual relationship” (Mohammadi & Khaleghi, 2018, p. 141).

It is apparent that the objective is to fix, correct, or treat gender dysphoria by reconditioning a transgender subject through a cultural and social context. Ultimately, the study’s goal is for transgender subjects to de-transition and accept their biological sex as their gender identity. In their study’s findings, Mohammadi & Khaleghi propose an approach to recondition transgender subjects through a social and sexual lens as well as promote conversion and reorientation, which are explicitly discouraged in literature discussing the ethical guidelines of performing studies that include transgender participants. Mohammadi & Khaleghi’s published findings also consistently use outdated terminology that pathologize transgenderism and imply that it is a “curable disorder.” Whether it be ignorance or motivation to erase transgenderism from mainstream culture, studies such as this take advantage of a vulnerable population, have the potential to cause a great deal of harm to participants, and invalidate their research findings. These studies should be immediately rejected by IRBs due to their ethical violations.

The question of the neurological basis of GI and transgenderism is a valid one, but the research on such topics must be carefully vetted to ensure that the methods, procedures, and goals of the study are ethical. There are studies that follow the ethical parameters laid out by *Transgender Health* and by Eric Lloveria Caselles in “Dismantling the Transgender Brain” (Adams et al., 2017; Caselles, 2018). Both of these articles are respectful and considerate of the involved participants, and they should be considered as excellent points of reference by neuroscientists conducting brain imaging studies--or any other kind of research--that include transgender participants. There are studies that adhere to the frameworks laid out in these ethical reviews that are changing the standards of research and care for transgender individuals (including Polderman et al., 2018; Caselles, 2021; and Uribe et al., 2020). These studies do not

pathologize gender incongruence, pass moral judgements, or misgender transgender study participants. Their goals are oriented toward scientific understanding rather than treatments or cures.

In closing, identifying the etiology of transgenderism necessitates the use of between participant comparative studies contrasting the brains of trans- and cisgender individuals. While the nature of such studies is not inherently injurious, a great deal of caution should be taken to prevent bioethical justice violations as well as to affirm gender identity in transgender participants. Non politically correct gendered language, unnecessary binarizing, and pathologizing terminology are unacceptable and preventable when researchers invest in gender identity studies and the research is adequately reviewed by respective IRBs. Consulting transgender people to self-educate and prioritizing participants' health and well-being over scientific interest is of the utmost importance in comparative brain imaging studies. This is the responsibility of affiliated researchers and IRBs. It is critical that rigorous ethical research be done to aid in the establishment of protective measures and ensure the mental and physical well-being of transgender persons as a vulnerable minority population.

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