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Sex and the brain across the lifespan

Reporting, discussing and interpreting sex differences in clinical and biomedical research has become a more complicated task in recent years, but necessarily so. Achieving clarity around what constitutes sex and what is associated with gender provides few conclusive answers and far more questions. As cogently expressed by Beans Velocci, a historian of sex and science, in a recent piece in *Cell* on sex as a scientific category, "…because it is so many things at once, all we can say for sure about what sex *is* is what a given scientist does with it" (B. Velocci, *Cell* 187, 1343–1346; 2024).

Indeed, in considering work in mental health research, where the lines of inquiry include so many different methodologies, such issues about the accuracy and consistency of labels abound. To compensate for the discrepancies among definitions, the prevailing standard is that sex categorically refers to the biological domain, broadly characterized, for example, by anatomical, chromosomal and endocrinological distinctions. Gender is a construct that refers to roles and identity that are socially determined. Where humans are concerned, which is the majority of the content published in *Nature Mental Health*, the terms 'female' and 'male' are used predominantly as adjectives. In contrast, 'men' and 'women' are suggested terms for referring to people, along with descriptors such as nonbinary, cis, trans and intersex, where appropriate, to describe people in a specific dataset.

Nevertheless, it can be a challenge to decide what the best descriptors are and which terms should be used and in which contexts, and there is still potential for conflating whether observed differences are actually sex or gender based or where sex is a category of oversimplified groups. Therefore, the concerted efforts among research stakeholders to make even incremental improvements in experimental design, data collection and reporting that prioritizes sex as a biological variable are yielding some progress. These steps are also foundational to bolstering understanding of sex differences in the dynamic systems and processes that influence physical and mental health, such as endocrine function and brain development over the lifespan.

In a Comment in this issue, Heller et al. discuss the mission and goals of the ENIGMA Neuroendocrinology Working Group, which is seeking to narrow the knowledge gaps around the interaction between endocrine function and the brain and the drivers of increased rates of disorders such as depression. Fluctuations of hormones associated with sex, such as estrogen, androgens and progesterone, are implicated in brain development and functional trajectories, yet more work is needed to understand variation across female developmental stages: perinatal, pubertal, pregnancy and menopausal. The authors argue that leveraging advances in technology for incorporating 'mega-analysis' of imaging, genetic, behavioral and clinical data could lead to identification of the neuroendocrinological bases that contribute to sex disparities in the experience of mental health conditions.

This issue also features several primary research papers that provide new insights into specific windows of neurobiological function mainly in female participants during key developmental or transitional periods of life. There is a growing body of work showing that sex differences in the brain's cortical circuitry emerge prenatally and that maternal care, such as skin-to-skin contact, can influence neural signaling. Frohlich et al. investigated how neural complexity can change during the prenatal window. Brain development, especially during prenatal development and early life, is critical for mental health later in life. To accomplish the challenging task of recording brain activity in human fetuses and newborns, the authors used magnetoencephalography and recorded brain signals in response to sequences of auditory tones, showing that in both fetuses and newborns, neural complexity declined with fetal maturation and after birth, but did so faster in male fetuses than in female fetuses. These differences may shed some light on why certain neurodevelopmental disorders occur at different rates in boys and girls. Furthermore, these data suggest the use of neural complexity as a sex-differentiated *in utero* marker to assess healthy brain function and potential vulnerability.

Finding robust links between prenatal brain function and subsequent risk for developing mental health conditions may one day lead to the identification of potential interventions. Much more is known, however, about the associations between early-life exposure to stress and mental health, derived from longitudinal cohort studies and translational work. A related strand of research has demonstrated that stress during childhood and adolescence increases the risk of experiencing postpartum depression, although the underlying mechanisms are not clear. In a cross-species translational study, Niwa et al. provide parallel evidence in female humans and mice that the experience of stress during adolescence was associated with increased glucocorticoid production during the postpartum period; participants diagnosed with postpartum depression demonstrated sustained cortisol levels for at least 6 weeks after giving birth. These data provide new clues about the role of prolonged hypothalamic–pituitary–adrenal dysregulation during the adolescent and pubertal window in the pathophysiology of postpartum depression.

Even in studies investigating postpartum depression and reproductive and lactogenic hormones that are specific to the female sex, it is not possible to fully account for the heterogeneity of stress-related sources and experiences that might instead be attributed to gender. Girls and women are far more likely, for example, to experience trauma from sexual and physical abuse, owing to gender roles embedded within social and cultural circumstances. More work on understanding how the

interactions of gender- and sex-based differences affect brain development and underlie disparities in certain mental health conditions, such as post-traumatic stress disorder and depression, is essential.

In addition, there is little known about sex-based changes as a function of chronological age and whether those processes are distinct or overlap changes during developmental stages. Moreover, chronic physical disabilities that emerge later in life can also be associated with brain aging and cognitive decline. Chronic musculoskeletal pain is extremely common, being more prevalent and resulting in more severe clinical manifestations in women, particularly after menopause. In a cross-sectional and longitudinal study using UK Biobank data, published in this issue, Zhao et al. found that people with knee osteoarthritis were characterized by older brain age, a pattern that was associated with increased memory decline and dementia at follow-up. Because of the higher prevalence of chronic musculoskeletal pain in women, the study included age- and sex-matched participants to "capture a sex-neutral brain aging trajectory." This study provides a great example of considering the impact of sex and gender, even when it is not the primary focus of the study but can inform future work that explicitly examines sex differences.

Notably, for many studies, such as those that use large data repositories, questionnaire data often remain ambiguous, as the terms 'sex' and 'gender' have been used interchangeably. This reaffirms how vital it is to know the context in which a study was designed and initiated, the questions it seeks to ask, and the limitations that real-world data collection and use present to researchers. It also provides a reminder that striving for precision, accuracy and inclusion is more than the labels used, but is a crucial step toward improving health inequities.

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