

Preface

SEX DIFFERENCES IN BRAIN AND BEHAVIOR: An eddy of calm in the tempest? Has there ever been more turmoil over the issues of sex and gender than today? At the onset of civilization, men were so firmly in control, and so adamant about female submissiveness, that there was little open discussion about the role of women. Thanks to two centuries of feminism, sexist assumptions of the past have been so widely questioned that the trickle of grumbling has erupted in a waterfall of vigorous debate: the Me Too movement, the fight for female reproductive rights, the questioning of strictly binary gender identities, the transitioning of children away from the gender assigned at birth, the advisability of puberty blockers, whether special considerations for people who have a uterus is transphobic, and the inclusion of both sexes in medical trials and research, are examples of where our notions about sex and gender are in remarkable flux. Few would hazard a guess about how or when these issues will be resolved, if they ever are.

While open discussion and debate is crucial for a democracy, many questions about sex and gender have become increasingly polarized, amplified by “alternative facts,” the rise of both authoritarianism and anti-secular sentiment, and a long-simmering frustration with the slow pace of civil rights efforts. Anyone asking whether children voicing gender dysphoria should always be encouraged to transition immediately can expect vitriol from both activists who immediately label any hesitation as transphobic, and fundamentalist religious forces declaring any transition a perversion of Nature. Even within the confines of academia, where it is supposedly permissible to consider controversial ideas under the protection of academic freedom, tenured professors endanger their positions if they ask whether all pedophiles actually abuse children, whether taking a “wait and see” approach to children with gender dysphoria is preferable to immediate transition, or whether social influences can spread gender dysphoria among young adults.

Within this maelstrom of sex and gender, the half-century or so of debate about whether the differences in the behavior of women and men are due to differences in brain structure and/or function, whether circulating hormones contribute to those differences, and whether prenatal hormones help engender them, may seem staid and decorous in comparison. The chapters in this volume offer a variety of windows onto these more circumscribed issues while maintaining respect for divergent views and those who hold them.

For example, philosopher Cordelia Fine has a long history of skepticism about sex differences in the human brain and their significance for behavior, pointing out instances where these may have been exaggerated in an enterprise that incentivizes reporting of differences between groups rather than null findings (Fine 2017). In her chapter herein, she explicitly addresses the thorny issue of how to find the boundary when such critiques leave the realm of fair skepticism and cross into politicized discourse. Naturally, scientists who search for and report sex differences in the brain, versus those concerned that the significance of such reports are inflated by the public, may differ in their perception of where the boundary between reasonable skepticism and politically motivated denial falls. Objects in the mirror may be closer than they appear. Fine’s reasoned analysis of this question in three domains offers an important framework for both sides in the future.

That framework will only gather in importance if more, and more subtle, sex differences in behavior come to light, as Brian Trainor and Annegret Falkner predict will occur with the advent of machine-learning tools and “big data,” which are on the horizon. They argue that these approaches will provide a richer understanding of individual differences in behavior, both between and *within* the sexes, as opposed to traditional “single-variable” measures of complex behavior, which are typically

built upon assumptions that what males do represents a default. That approach can mask individual variability within the constraints of male behavior. Trying to squeeze the behavior of females into a box predicated on male behavior may not only gloss over important subtleties, but may also prevent researchers from understanding the adaptive significance of alternative behaviors.

That largely implicit consideration of males as the default has a long history in the biomedical literature, as Irving Zucker et al. point out, with the result that most of the accepted notions about the kinetics of drug treatment, based as they are on measures from only males, again tries to squeeze females into a male-biased box, exposing women to higher drug concentrations and more adverse reactions than males. The authors document how, despite the NIH mandate to include both sexes in research and trials, research from the past decade continues to neglect females.

Perhaps the most well-known overmedication caused by ignoring sex differences in pharmacokinetics is the excess dosage of the so-called Z-drugs as a sleep aid in women. James Walton et al. note that another important variable typically ignored in the conduct of research is the circadian rhythm, which interacts with sex, as they detail. The sex differences in chronotype, which begin at adolescence in humans, are in full display in animal studies where circulating gonadal hormones, rather than sex chromosomes, appear to be responsible. Lumping measurements from different phases of the circadian rhythm not only adds to variance that might obscure differences, but can again mask important behavioral adaptations.

Our current understanding of the so-called organizational influence of gonadal hormones on brain structure and function is expanded by Bruno Gegenhuber and Jessica Tollkuhn's exciting recent discovery that estrogen receptors can induce a long-lasting sex bias in gene expression in the bed nucleus of the stria terminalis, with implications for other brain regions involved in social behaviors, including sexual and parental behavior. They map out a program for how to explore which regions display similarly sustained epigenetic changes, and how those changes interact to affect behavior.

One of the most prominent and persistent sex differences in human disorders is the greater risk of major depressive disorder (MDD) in women than in men. Elizabeth Williams et al. probe the roots of this sex difference in preclinical studies of rodents, focusing on a particular brain circuit, from the ventral hippocampus to the nucleus accumbens, where sex differences in excitability appear to underlie sex differences in behaviors, offering a strong parallel to sex differences in human MDD. They speculate that a better understanding of sex differences in this circuit could offer improved diagnosis, prevention, and treatment of depression and other mood disorders.

An important factor in depression is stress and, despite the trope that only death and taxes are certain, we can surely add stress as another inevitability of life. Here again, sex differences are prominent, perhaps because of sex differences in reproductive strategy and, especially in mammals, sex differences in parental investment. As Robert Handa and colleagues explain, the activation of the hypothalamic-pituitary-adrenal axis (HPA) in response to physical stressors is generally greater in females than males among mammals, but in humans, where stress tends to be psychological—at least in laboratory studies—men show greater activation of the HPA. They also relate recent explorations suggesting that gender identity is another factor in responding to stress, and call for studies of the interaction of chromosomal sex and gender identity to better understand the stress response.

Another crucial response to stress involves the innate immune system, including the mast cells that orchestrate defenses, but can sometimes overreact, with consequences for many inflammatory and stress-associated disorders, including autoimmune diseases and migraines. Emily Mackey and Adam Moeser lay out preclinical research that begins to parse the role of sex differences in mast cell response, which could underlie the prominent sex differences seen in many of these disorders. They find strong evidence that circulating gonadal steroids modulate mast cell responses, and that these same hormones exert a longer-lasting effect in the perinatal period.

Evidence for the influence of gonadal hormones in the perinatal period on human sexual orientation and gender-typical behavior is explored by Ashlyn Swift-Gallant et al., exploiting indirect

markers for prenatal androgen influence—digit ratios—and a clinical syndrome in which prenatal hormone levels are sex-typical in early fetal development, but largely absent in the period just before and after birth. Together, these data offer evidence that androgen exposure in the early fetal period can promote sexual attraction to females in adulthood, while androgen levels in the late perinatal period affect childhood gender conformity, and estrogens in the later perinatal period may augment attraction to men in adulthood.

Because most of the sex differences in behavior common in mammalian species, such as in aggression, dominance, and territorial defense, are reversed in the spotted hyena, these outliers offer a fascinating insight into the evolutionary forces driving those sex differences. S. McCormick et al. provide an overview of the literature about these beautiful, fascinating, and ferocious animals, arguing that a critical distinction for understanding the evolution of the sex reversals is between behaviors related to *access* to food, rather than those related to *acquiring* food.

Arthur Arnold concludes the volume by calling for a greater appreciation for the role of chromosomal sex in the training of future scientists exploring sex differences in brain and behavior. Explicating the influence of mammalian sex chromosomes, and their fascinating evolutionary history, as well as the alternative systems of sex determination in other vertebrates, will provide a richer understanding of sexual differentiation in all its domains, and better prepare future researchers.

Since the onset of this book project, we have lost two outstanding scientists who were also devoted mentors and wonderful people. A student of Donald Hebb, Stephen E. Glickman never lost his sense of wonder about animal behavior, studying animals in zoos and an astonishing variety of mammals, including skunks, gerbils, lizards, wood rats, and those amazing, gender-bending spotted hyenas. Heading up a massive project to capture hyena pups in Kenya to create a pack roaming a semi-naturalistic compound in the hills of Berkeley, California, Steve was perhaps the only person who was so fluent in the languages of psychologists, endocrinologists, evolutionary biologists, and field ecologists to successfully coordinate this massive project that informed many of the discoveries reported in McCormick et al.'s chapter herein, for which Steve was a coauthor. Steve was also an excellent colleague for both the editors in their years at Berkeley. A gentle, self-deprecating man with a wonderful smile and a truly vast breadth of intellectual interests, he passed away unexpectedly at 87.

We also shared a personal history with Robert J. Handa, who was a graduate student in anatomy while we were psychology graduate students at UCLA. Bob was a keen observer and critical thinker who realized that studies relying upon 5- α reduced metabolites of testosterone such as dihydrotestosterone (DHT) to stimulate only androgen receptors were working from a flawed assumption. Through his careful analyses, Bob documented metabolic pathways that could convert DHT to ligands active at estrogen receptors, providing a vital corrective to the literature (unfortunately, not everyone got the memo). We fondly recall his grace and ready smile in every situation, and mourn his passing much too soon at the age of 67. In addition to his prolific research career, Bob was an avid fisherman and the ultimate mentor. On his final fishing trip, fully aware of his grave prognosis, Bob was pleased that his contribution to this volume, the last manuscript he completed, would help his students' careers. Would that we all had such considerate and supportive mentors, and may all who follow after us be so blessed!

We thank Richard Sever for inspiring this volume and Barbara Acosta for her guidance, patience, and good humor—despite the pandemic—and all our authors for their dedication to a better understanding of what it means to be a human of any gender.

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REFERENCE

Fine C. 2017. *Testosterone Rex: myths of sex, science, and society*. W.W. Norton, New York.