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Sex/Gender Influences on the Nervous System: Basic steps toward Clinical progress

Claudette Elise Brooks[1] and **Janine Austin Clayton**[1]

[1]Office of Research on Women's Health (ORWH), Office of the Director, National Institutes of Health (NIH)

Abstract

A commentary highlighting the progress that sex-based data and research have made in neuroscience and the complexities that research has revealed thus far. Basic and preclinical neuroscientific research that considers sex as biological variable will continue to build on the foundation of knowledge that has been started by multiple predecessors. The expansion of knowledge in preclinical neuroscience that integrates the study of both sexes will have a significant role in informing clinical trial design. We applaud the editors and authors efforts who have contributed to this issue.

Keywords

Women's Health; preclinical research; biological variable; reproducibility; sex-based data

Neuroscience is one of the most riveting, promising, and challenging areas of biomedical research. New technologies and burgeoning scientific advances have unearthed complex mechanisms and catalyzed discoveries about how the central and peripheral nervous systems play complex roles in homeostasis at the organism level and influence overall health and disease. Inter-species variability and inter-individual variations in connectomes, function, and plasticity are just a few domains that contribute to the high degree of heterogeneity displayed in nervous system form and function. Recognizing differences and discerning which differences are important is a hallmark of the scientific method, where we control for, or test the effects of, important variables which may affect outcomes. Sex is a primary domain of biologic variability and accounting for sex as a biological variable is fundamental to rigorous, and relevant biomedical research.

Preclinical research to date has been primarily conducted on male animals or without transparent reporting of sex (Beery 2011; Yoon 2014). Though cell-based studies are critical

Corresponding Author: Claudette Elise Brooks, MD, Office of Research on Women's Health, NIH, 6707 Democracy Blvd, Suite 400, Bethesda, MD 20892, Phone: (301) 402-1770; Fax: (301) 402-1798, Claudette.Brooks@nih.gov.

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in basic science research, recording the sex of origin and reporting sex-based data are too often left undone in primary cell and tissue culture and *in vitro* cell line studies (Park M-N 2015). The past two decades have ushered in an increased awareness of the influence of sex on neurobiology and neurophysiology. Today, new research evidence unlocked via application of a sex/gender perspective to neuroscientific investigation has triggered enhanced stakeholder appraisal of the influence of sex as a biological variable and elevated the regard with which these issues are held driving the field to a tipping point, beyond the margins toward mainstream neuroscience. Indeed, these considerations are not an add-on but critical components of building an evidence base.

The heightened incorporation of this variable into animal models can generate data with the power to both transform our understanding of male and female biology and pathophysiology and inform clinical research. This expansion will have its difficulties, including investigators new to considering sex as a variable in their research, and adopting and adapting methods to their specific scientific discipline and hypotheses. To fulfill expansion of the neuroscience knowledge base, research results must be disaggregated by sex and analyzed and interpreted in the context of sex as a biological variable. Beyond describing differences and equally important, the lack thereof, comparing *and* contrasting results by sex and routinely providing descriptive statistics by sex are sorely needed. The reviews including *Sex differences in animal models and decision making* (Orsini In press), *Sex differences in non-human primate behavioral development* (Lonsdorf In press), and *Translational value of female rodent social stress models: are we missing the mark?* (Solomon In press) explore the use of animal models in various areas of neuroscience and the challenges posed in translation to humans in biomedical research.

The Office of Research on Women's Health (ORWH) in the National Institutes of Health (NIH) Office of the Director, along with NIH's 27 institutes and centers, has worked for over twenty-five years towards putting science to work for the health of women. Efforts like this issue of Journal of Neuroscience Research (JNR) are critically important and aligned with NIH policies released in 2015 and implemented earlier this year on Enhancing Reproducibility through Rigor and Transparency (NOT-OD-15-103) and a portion of that policy specifically, Consideration of Sex as a Biological Variable in NIH-funded Research (NOT-OD-15-102). The guidelines to JNR have been amended to improve reproducibility and JNR is now an endorsing journal for principles and guidelines for reporting preclinical research.(NIH) This themed issue of JNR on sex/gender influences on nervous system function represents another crucial step forward in providing the pathways for sex/gender-informed basic science and preclinical research questions to be asked and answered and delineation of sex and gender influences in health and disease beyond similarities and differences. This issue additionally signals a momentous change in the journal's policy, all publications in the future will be required to state the sex of the animals/subjects in the title and/or abstract.

Sex is based on biology –derived from sex chromosomes and corresponding gonadal structures, and declared at birth (natal sex: male, female). Gender is a psycho-social construct that encompasses how one views oneself, or gender identity (e.g. man, woman, gender diverse person) and the societal and cultural context which assigns certain roles

(gender role) and behaviors to individuals that typify male (masculine) or female (feminine) traits. In humans, sex and gender are intertwined and difficult at times to tease apart (Clayton 2016). Research involving and considering the impact of sex and/or gender is not inherently 'sex differences' research. Sex/gender *influences* research considers the impact that sex or sex-based biology and gender may have on the hypothesis, experimental design, analysis, and the interpretation and reporting of results. It employs a balanced approach by studying both males and females as appropriate for the research in the context of the scientific question under study. While not necessarily powered to detect sex differences, such approaches can provide much needed and informative sex-based data. Research on sex *differences* goes a step further being specifically designed to uncover and characterize male/female differences and powered to detect and quantify data to elucidate any statistically significant differences between males and females (Clayton 2016). An investigative approach that accounts for sex as a biological variable operates as a lever of enhanced rigor to uncover mechanistic understanding, and expand the relevance of research results.

Sex and gender influences have been noted across the nervous system and epidemiologic and clinical differences are self-evident. Interwoven biological and social factors have implications for precision-based therapies for women and men and these factors can interact having mitigating, moderating, and sometimes mediating effects. Disease and disorders such as multiple sclerosis (MS), anxiety, depression, pain/pain syndromes, and Alzheimer's dementia/cognitive impairment are among those that occur predominantly in women (Pankevich 2011).

Ischemic stroke is among the top causes of morbidity, disability and mortality globally. Women have a higher stroke burden and having a stroke has a disproportionately negative post-stroke impact on women (Go AS 2013; Statistics 2012). The higher rates of lifetime risk, disability, institutionalization, poorer outcomes, and mortality, cannot be explained by social health determinants, although they are contributory. In previous investigations by Louise McCullough has reported neuronal utilization of distinct cell death pathways in a mouse model of ischemic cell death (McCullough 2005). In this issue *Sex differences in stroke therapies* (Sohrabji In press) explores the basis for altering stroke treatment algorithms.

Autoimmune and neuro-immunological disorders can adversely affect nearly all of the functional portion of the CNS. Although they occur in both men and women, women predominate for most of the adult-onset disorders. In the 2011 IOM *Sex differences and implications for translational neuroscience research: Workshop summary*, MS and neuroinflammation were one of the recommended four priority areas in neurologic disease for sex differences research (Pankevich 2011). MS affects women 2–3× more than men, most notably in the child-bearing years with average clinical onset between ages 15 to 45 years (Ramagopalan SV 2011). However, in some forms of progressive MS men represent a larger proportion of MS patients as compared to the relapsing/remitting form of disease (Koch 2010; Voskuhl 2012; Wolinsky 2009). In earlier preclinical research utilizing multiple murine strains in experimental autoimmune encephalomyelitis (EAE), a frequently studied model for MS, it was found that sex differences in severity varied by genetic strain(Papenfuss 2004). Diseases such as systemic lupus erythematosus (SLE) can

secondarily involve the CNS (CNS Lupus or cerebritis) and manifest its pathophysiology as a vasculopathy, autoantibody generation, or other clinical syndromes. It occurs in women and girls of all ages more than in men and boys. SLE in women of childbearing age occurs in a ratio of 7.1–15.1 to 1, women to men (Chakravarty EF 2007; Lahita 1999). The etiology of these disabling neurologic disorders remain elusive disabling adults often in their most productive years. Explicating the underlying mechanisms of sex differences in these immune-mediated diseases represents a rich opportunity for exploration and discovery. The research presented in *Single nucleotide polymorphism rs948854 in human galanin gene and multiple sclerosis: a gender risk factor (Lioudyno In press.)* is one example of how genetics may play a role in understanding this disease. The research reviewed and highlighted in *Sex differences in neuro-immunity and pain* (Rosen In press.), *The immune system as a novel regulator of sex differences in brain and behavioral development* (Nelson In press), and *Sex differences in the neuroimmune modulation of memory* (Tronson In press), along with the hypotheses generated by that research, may shed light on the answers or the methods that should be used in the approach.

There have been a cadre of dedicated investigators that have worked in the study of sex differences in neuroscience and other biomedical disciplines for years advancing the field, and some of them have contributed to this issue and others similar to it over the years. Their steadfast investigations have generated foundational data. Building a skyscraper requires digging a deep foundation. We need to dig deep to go higher! There is a high degree of variability of uptake of sex/gender considerations by scientific discipline. We applaud the editors and authors for focusing upon critical sex and gender factors in neuroscience and for the comprehensive approach taken in this special issue. Such galvanizing efforts have the power to change our research results from data that informs into data that transforms, turning knowledge into action.

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Significance Statement

Sex is a primary domain of biologic variability and accounting for sex as a biological variable is fundamental to rigorous, and relevant biomedical research. Preclinical neuroscientific research on sex influences has made significant gains and is expected to inform clinical research leading to better health for women and men.