

Sex-related variations in neuroscience and endocrinology and their effects on mental health

Should you be taking into account the sex of your client when considering diagnoses, interventions or treatment plans? If so, how would you go about doing this, and what factors should you consider?

In counselor training programs, we are often taught that differences exist in prevalence rates among males and females for certain disorders. We are at times encouraged to consider sex when deciding criteria for membership in group counseling, particularly when running offender or survivor groups, for safety purposes or when it might simply feel more comfortable for participants. This article takes the question of sex differences one step further by exploring various explanations for potential sex differences and asking whether sex-related variations in brain structure and function, autonomic arousal and endocrinology (primarily levels of sex hormones) should factor into client care.

It is important to note that in this article, I am speaking to biological sex, which is influenced by chromosomal variations and levels of sex hormones. In doing so, I am not suggesting that a binary, sexually dimorphic categorization should be the basis for differentiation, but rather that sex-related variations in brain and physiological functioning may play an important role in mental health and efficacious counseling interventions.

Sex bias in research

Sex bias is a long-standing issue within a multitude of fields related to mental health. Bias is often present in the selection of research design, assessment measures and practices, diagnostic criteria, the sex of participants and in the analysis and interpretation of data. In 1992, Linda Gannon at Southern Illinois University at Carbondale suggested

that as early as the 1970s, supporters of the feminist movement stressed the importance of developing inclusive models of human, not simply male, behavior. However, it was not until 1993 that the National Institutes of Health (NIH) Revitalization Act mandated the inclusion of females in human clinical trials. However, this mandate did not cover the use of females in nonhuman research (e.g., rodents).

Given notable fluctuations in female endocrinology over the estrous or menstrual cycles (depending on species), females were often deemed too problematic to include in highly controlled scientific research. In 2011, Annaliese Beery and Irving Zucker at the University of California—Berkeley contested this notion, reporting that eight of 10 biological fields still contained male sex bias in nonhuman biomedical research. This difference was most notable in neuroscience, with males outnumbering females by a 5-to-1 ratio and nearly 40 percent of studies not reporting sex. Pharmacology (a 5-to-1 ratio) and endocrinology (greater than a 3-to-1 ratio) also contained notable bias. Similarly, Kelimer Lebron-Milad and Mohammed R. Milad reported that although a significant amount of literature detailed learning, memory and fear extinction relevant to anxiety and posttraumatic stress disorders (PTSD), less than 2 percent of research included females.

By using only male mammals and relying solely on male brain structure, physiology and endocrinology, we build misleading models of addiction, stress and other issues that can distort behavioral and pharmacological interventions. Exclusively using male animals can also hinder researchers in identifying possible variations in responding that may be

revealed only in the presence of both sexes. As the field of mental health moves forward, it will be important to consider sex-related neurophysiological variables in the etiology and symptom presentation of disorders and the best practice care of clients.

Sex differences in mental health

Debates surrounding sex and gender differences are notable in mental health. Women have historically been considered more emotional and emotionally labile, while men were thought to be more mentally tough, rational and physically oriented. Today, we still see these antiquated gender role distinctions perpetuating the stigma around males, in particular, seeking counseling. Notwithstanding (and at times owing to) such historical portrayals of males and females, sex differences in the prevalence of certain mental health disorders remain. Autism spectrum disorders (ASDs), conduct disorder, attention-deficit/hyperactivity disorder (ADHD) and schizophrenia tend to be higher in males, whereas females experience higher rates of mood disorders, PTSD and anorexia nervosa. Even within certain disorders such as substance abuse and PTSD, we see variations among males and females.

With addiction, general differences exist in the reasons that males and females start using. Males tend to initiate use in an effort to engage in more risky behavior and derive positive reinforcement, whereas females tend to initiate use to alleviate (largely psychosocial) stress. Similarly, childhood maltreatment may be a stronger predictor of adolescent substance use in females. Females also tend to transition into addiction more rapidly. The effects of stimulants can also be different for females and males, with a female's response varying over the

menstrual cycle. The menstrual cycle can also influence attempts at quitting and relapse, with stronger cravings taking place during the luteal phase when estrogen and progesterone decline.

Marked differences also exist with PTSD. Females are twice as likely as males to develop PTSD, with symptoms lasting four times longer, even though males on average experience more traumatic, and often more violent, events throughout life. Furthermore, female survivors of interpersonal violence develop PTSD six times as often. Examination of PTSD symptoms indicates that males tend to experience more anger and reexperiencing symptoms, whereas females likely experience more emotional numbing, restricted affect, avoidance responses and somatization. Females also experience greater psychological reactivity to traumatic stimuli and report feeling more shame and diminished belongingness.

However, researchers often muddle the concepts of sex and gender. This mislabeling can incite confusion and lead to difficulty in teasing apart the various sex-related contributing factors to mental health. Thus, in the examination of *sex*

differences in mental health, it has been challenging to parse out nature from nurture, or ingrained, culturally defined gender stereotypes from physiological variations.

The interchangeable use of the terms *gender* and *sex* in literature underscores such difficulties and has created a heated debate around this topic. One side insists that attempting to delineate differences between males and females only perpetuates ethnocentric gender biases, whereas the other side emphasizes the importance of considering differences to improve mental and physical health interventions. Given advances in technology, there has been a recent reinvigoration of research investigating how differences in gene expression, patterns of development and connection between brain structures, and endocrine variations in and across males and females influence emotion, behavior, cognition and the prevalence and expression of mental health disorders. What follows is an overview of some of the recent findings and how they may apply to your work as counselors, counselor educators or clinical supervisors.

Sex differences in neurophysiology

Differences between male and female brains related to structural development and patterns of connection become conspicuous during adolescence with the influx of sex steroids such as androgens (e.g., testosterone) and estrogens. Other differences are present in genetic expressions that occur even before birth. Research led by Yale University's Nenad Sestan found that nearly 80 percent of the genes that are differentially expressed between sexes during the prenatal period are in males and have been linked to disorders such as schizophrenia and autism.

In a recent meta-analysis of sex differences in brain structure, Amber Ruigrok and her team from the University of Cambridge noted that males on average have a larger overall brain volume (taking into account body size) and a greater volume of white matter (the myelinated axons connecting neuronal cell bodies). Differences were also present in the regional volume of specific areas. In more than 2,000 brains, males (ages 7 to 80) on average had a larger gray matter volume in the right and left amygdala, putamen



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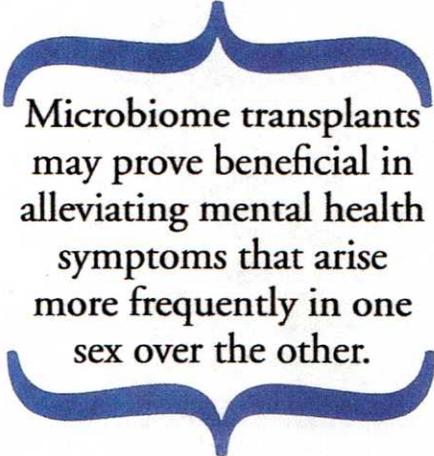
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(involved in limb movement, some forms of learning, dopamine regulation and addiction) and posterior cingulate gyrus (which may play a role in the default mode network, or resting state activity in the brain, and has been implicated in ASD, ADHD and schizophrenia). Females often have a larger insula (involved in empathy, socioemotional processing, somatosensation, interoception and pain perception), thalamus and anterior cingulate cortex (active in emotion regulation, socially driven interactions, empathy-related responses and decision-making).

Variations have also been noted in the patterns of connectivity between brain regions. Earlier this year, researchers from the University of Pennsylvania School of Medicine detailed the use of diffusion tensor imaging to examine patterns of connection between brain areas in more than 900 males and females ages 8 to 22. Led by Ragini Verma, the team found that the connectome (the pattern and strength of connection between various subnetworks of brain regions) differed between males and females, with differences increasing through late adolescence. These differences help explain some of the cognitive and behavioral strengths in males and females. For example, males' enhanced motor and spatial skills reflected stronger structural connectivity in motor, sensory and executive functions. Females showed enhanced memory and social cognitive skills associated with stronger brain connectivity between areas related to social motivation, attention and memory.

Sex differences are also present in cerebral blood flow (CBF), functional anatomy and neurotransmitter levels. Females have increased CBF compared with males, with CBF shifting in response to circulating hormones. A higher CBF suggests that females may be better equipped to effectively and efficiently circulate psychotropic medications throughout their brains. CBF abnormalities have also been linked to depression, addiction and schizophrenia.

Males and females also show differential activation of the hypothalamic-pituitary-adrenal (HPA) axis — part of our stress response mechanisms that help to activate the fight-or-flight systems — and secrete different levels of stress hormones



Microbiome transplants may prove beneficial in alleviating mental health symptoms that arise more frequently in one sex over the other.

following the same stimulus. Females have a more responsive HPA axis and higher cortisol secretion after stress. This level of reactivity can also vary with the menstrual cycle. The HPA axis plays a role in anxiety, PTSD, depression, immune functioning and so on. These differences can also affect the functioning of the paraventricular nucleus, which has a role in reward conditioning and drug-seeking behavior in addictions. Furthermore, females have higher serotonin levels, but males synthesize serotonin faster. Again, these variations can influence differential rates of depression between sexes. The functioning of dopamine and oxytocin are also heightened in females. Dopamine plays an integral role in the brain's reward centers, reinforces the effects of many drugs and is implicated in schizophrenia.

Sex differences in the microbiota-gut-brain axis

Given the burgeoning research detailing the impact of gut microbiome on brain and mental health functioning, examining sex differences in the microbiota-gut-brain axis also proves quite interesting. The microbiome experiences developmental stages similar to that of the brain, with sex differences emerging during puberty and continuing into adulthood.

Males experience relatively stable microbial communities, while the female microbiome varies with cycling hormone levels. With decreasing levels of ovarian hormones, as the microbial community shifts, females are at an increased risk for mood disorders, sensitivity to pain and gastrointestinal difficulties. Not only do hormones influence the bacteria in

the gut, but the bacteria directly impact levels of hormones and neurotransmitters such as serotonin, dopamine and norepinephrine.

Eldin Jasarevic, Kathleen Morrison and Tracy Bale reported that the transfer of the contents of an adult male mouse's caecal (beginning of the large intestine) into a pubertal female mouse masculinized the composition of the microbiota and elevated testosterone levels. These changes persisted into adulthood. Similar caecal transplant studies demonstrate how the introduction of new microbial communities can alter behavior, with the recipient's behavior taking on more of the behavior of the donor. Jasarevic and his colleagues suggest that microbiome transplants between males and females may prove beneficial in alleviating mental health symptoms that arise more frequently in one sex over the other.

Role of sex hormones

Interestingly, levels of circulating sex hormones influence nearly every single one of these variations between males and females. Blood flow, HPA axis functioning and levels of neurotransmitters are all regulated by gonadal steroid levels. Sex hormones are also thought to influence plasticity by way of myelination, the branching of dendrites and the formation of new synapses. Estrogen increases CBF as well as levels of 5-HT (serotonin receptors), dopamine and oxytocin. Given that estrogen enhances 5-HT neurotransmission, it also may accelerate the response to selective serotonin reuptake inhibitor treatment. Increased levels of estrogen and testosterone both enhance the functioning of the HPA axis and related corticosterone release and negative feedback loops.

Several studies have shown the protective benefits of testosterone in stress responses and a range of mood disorders. Similarly, estrogen serves as a protective factor against developing PTSD and anxiety disorders, and it also enhances fear regulation. So, in essence, where a female falls in her menstrual cycle at the time of a trauma may in part influence how likely she is to develop PTSD. In other words, a woman who experiences a trauma just prior to ovulation, when estrogen levels peak, may be more psychologically resilient to the trauma

than if that trauma occurred when her estrogen levels were lower.

In a provocative 2012 article, researchers Nikole Kirin Ferree, Malinda Wheeler and Larry Cahill reported that the use of emergency contraception, namely Ogestrel (a combination of exogenous estradiol and progesterin), following sexual assault was associated with decreased posttraumatic stress symptoms. In addition, a team of researchers led by Enrique Baca-Garcia found that female suicide attempts increased when levels of estrogen and progesterone were low (early follicular phase) and that these attempts were more severe.

This is just a selection of the extensive research in this area. Although quite complex and at times contradictory, research detailing the effects of sex hormones on symptoms of mental health disorders is a quickly expanding area of study. It may very well lead to novel counseling interventions and supplements to talk therapy for a range of disorders.

Sex-specific psychotherapy?

In 2015, the federal budget dedicated \$215 million to the growing field of precision or personalized medicine. This represents a move away from the one-size-fits-all model of care and embraces the discovery of new therapies from which to select when determining the best intervention for a particular client. This followed on the heels of the NIH's 2013 BRAIN (Brain Research through Advancing Innovative Neurotechnologies) Initiative, which is helping to revolutionize how we understand the human brain and thus prevent and treat a range of mental health disorders.

Glenda Gillies and Simon McArthur from Imperial College London have

argued the need to better understand the role of estrogen and sex-related differences in mental health functioning and called for the use of this information in designing hormone-based therapeutic agents for both males and females. This is just one of the many potential implications that can be derived from the study of sex differences in the brain and related physiology.

However, Daphna Joel at Tel-Aviv University and her colleagues caution readers not to think of sex differences as a dichotomy, but rather as a complex and unique "mosaic" of differences related to sex, with more features common to males or females.

Implications for counselors

As research advances, we as counselors can benefit from understanding the implications of this knowledge base on how we assess, conceptualize, diagnose and develop treatment plans for clients. For example, if we know that aberrant levels of estrogen may be influencing the presentation of a symptom, we may find it beneficial to work with that client in a different manner rather than responding to long-standing gender stereotypes without such aberrations in hormone levels.

At this point, this approach is speculative, but it will be interesting to see how research progresses in terms of related clinical implications and how, perhaps, the therapeutic relationship and associated clinical interventions may play a role in this neurophysiological dynamic. Based on the currently available findings, what may be beneficial is to provide psychoeducation around the effects of sex steroids on mental health functioning. By doing so, we can empower clients to recognize that the functioning of their

entire physical body has an impact on their mental health.

It may also be beneficial to work with allopathic, osteopathic and functional medicine practitioners to provide the best care for your clients. For example, if you are working with a male client with notable symptoms of depression, it may be beneficial to have him see a physician to assess testosterone levels as an adjunct to your ongoing counseling work.

Whether you believe that highlighting sex differences only perpetuates the problem of sex discrimination or you are eagerly exploring such variations, it is my hope that this article will help you stay informed about developments in this line of research and trends in the broader mental health world. Such knowledge allows counselors the opportunity to stay at the forefront of emergent mental health interventions and remain leaders among practitioners in mental health fields. ♦

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