HHS Public Access

Author manuscript

Biol Psychiatry. Author manuscript; available in PMC 2017 March 29.

Published in final edited form as:

Biol Psychiatry. 2016 November 15; 80(10): e81–e83. doi:10.1016/j.biopsych.2016.09.009.

Sex Differences and Personalized Psychiatric Care

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A single mother who has struggled in the past with anxiety and depression has healthy 12-year-old twins and asks when her son and daughter might develop similar symptoms. Specifically, she's concerned that her daughter has recently been more worried about school. You embark on the familiar conversation that both children are at familial risk. The patient, however, presses on that she wants to know what she might expect with each child and, specifically, whether her daughter might be at increased risk compared to her son. How might you discuss with her both the epidemiological data that support her concern and also the various neurobiological mechanisms that might underlie the reason her daughter is at higher risk?

Personalized medicine—the concept that an individual's unique characteristics can be used to tailor medical practice—is increasingly recognized as one of the next critical advances in biomedical research and health care. This requires understanding how genetics, epigenetic modifications, biomarkers and endophenotypes, and environmental factors influence individual disease risk and treatment response. Like other specialties, such an approach has promise in psychiatry (1). As increasing emphasis is placed on this concept of tailoring treatment based on differential disease susceptibility, risk, and outcome, two of the most globally recognized categories of difference have been previously overlooked: sex and gender (2).

The differential genetic, hormonal, and anatomic processes underlying typical sex development (i.e., sex differences) has been a significant scientific pursuit. In certain medical specialties, including endocrinology and obstetrics and gynecology, these processes have been used to develop effective medical treatments incorporating markers of biologic sex (e.g., oral contraceptives for pregnancy prevention or polycystic ovarian syndrome). However, while sex differences have been thought to partially explain observed differences in the development, emotions, and behaviors between males and females, the study and translation of sex differences in neuroscience and psychiatry has been challenging. Like other specialties in medicine, modern psychiatry was built on a history in which scientific advancement was often challenged by prevailing societal and scientific norms (3). For females, psychologic distress was historically considered to be wholly caused by anatomic and hormonal correlates of biologic sex, leading to certain psychiatric treatments through gynecologic procedures, including the removal of female reproductive organs (3). As

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medicine progressed and was influenced by social movements of the early 20th century, there grew greater understanding that social and cultural context associated with maleness and femaleness (i.e., gender differences) was a likely contributor to the development and presentation of psychologic distress.

The recognition that sociocultural factors must be considered alongside biological factors when discussing sex and gender differences in the prevalence and diagnosis of psychiatric diagnoses has allowed for better conceptualization of psychologic distress in clinical settings; however—and in contrast to earlier psychiatric research—such complexity has challenged researchers. Quite simply, it is easier to allow participants to self-report gender rather than perform karyotyping or sex steroid assays that provide biologic markers of sex. Convention in research failed to appropriately acknowledge sex, resulting in the use of only male cell lines or animals, as well as limited guidelines for reporting sex differences. This has not only led to significant gaps in drug development, with women comprising a greater proportion of adverse drug reactions compared with men (2); it has also brought to light the myriad ways sex and gender may influence mental health. Indeed, studying sex differences requires consideration of 1) differentiating between chromosomal and hormonal contributions when defining sex; 2) understanding how societal and cultural influences of gender and gender roles independently impact development, including through biologic mechanisms, such as epigenetic modification; and 3) the infrastructure and resources to perform research that appropriately accounts for the complexity of sex and gender differences (4).

Despite this history, there has been a renewed emphasis on understanding the critical contribution of sex and gender in neuroscience and psychiatry in recent years. In 2010, the Institute of Medicine convened an interdisciplinary workshop to discuss the importance of sex differences in translational neuroscience, stating simply, “In the current era of translational research and personalized medicine, it is increasingly important to take sex differences into account, so that the potential effects of products and therapies can be more fully understood” (4). In addition, in 2014, the National Institutes of Health began developing policies to ensure the inclusion of sex and gender in preclinical research (5). Since these milestones, an increasing body of neuroscience research has included sex, with several translational studies noting therapeutic implications. For example, one recent study among females with treatment-resistant schizophrenia noted reduced symptom severity and increased probability of clinical response when antipsychotic treatment was augmented with the selective estrogen receptor modulator raloxifene (6). Another study found a reduction in depressive symptoms and associated metabolic and neural network changes among females with major depressive disorder when escitalopram treatment was augmented with creatinine monohydrate (7). These studies, along with others, provide exciting advances leading toward personalized psychiatric care informed by sex and gender.

At the same time that sex and gender differences are being investigated to a greater extent among adults, it has been well established that there are sex differences in brain development among typically developing adolescents (8) and in the onset and severity of certain psychiatric illnesses, including depressive and anxiety symptoms (9). Both gray and white matter mature earlier in females along different developmental trajectories (8).

Females are also more likely to develop symptoms of depression and anxiety during adolescence compared with males; these differences are thought to be caused by a combination of genetic activation and hormonal effects arising during puberty, as well as environmental stressors associated with female gender (9). Because of the opportunity for effective intervention earlier in the disease process, sex and gender differences in the presentation and development of psychologic distress must be examined. This is a notable component of the National Institutes of Mental Health Research Domain Criteria—the framework for personalized medicine in psychiatry (1). Specifically, the Research Domain Criteria emphasizes the need for research to "Specify the mechanisms regarding developmental changes in systems for fear and distress across puberty (including the effects of the social environment), that could explain the peak onset of internalizing symptoms in adolescence and their correlation with puberty."

In this issue of *Biological Psychiatry*, Kaczkurkin *et al.* expand on research showing the differential vulnerability among adolescent females to mood and anxiety symptoms (10). Investigators used arterial spin labeling, a magnetic resonance imaging technique measuring blood flow, to examine cerebral perfusion among male and female adolescents 12 to 23 years of age, some of whom met criteria for lifetime psychopathology by DSM-IV criteria. Cerebral perfusion in a set of regions relevant to affective processing—the bilateral insula, left fusiform gyrus, and left amygdala—was associated with trait anxiety, and this association differed by biologic sex. Specifically, males showed decreased perfusion in these affective regions with age, whereas females showed increased perfusion, such that perfusion was significantly greater among females in the postpubertal period. Notably, greater left amygdala perfusion mediated the relationship between pubertal status and increased trait anxiety in postpubertal females. These results were not found with state anxiety, nor did amygdala perfusion differ across psychiatric diagnoses. Based on these results, the authors posit that affective neurocircuitry perfusion, particularly in the left amygdala, may represent a biomarker for the particular vulnerability of females to developing depressive and anxiety symptoms during adolescence and young adulthood.

The immediate implications of Kaczkurkin *et al.*'s study for personalized psychiatric care are expectedly limited given the infancy of exploring sex and gender in neuroscience. Indeed, the authors caution against the interpretation that the presented effects are directly caused by biologic sex, because adolescent females also have greater social cognition. Such socially relevant experiences, including experiences that may be associated with physical and sexual maturity, may interact with biological processes to influence amygdala perfusion and mood symptoms. However, this study underscores the critical importance of examining sex and gender differences, particularly during development. Such research lays the groundwork for additional investigation regarding how genetic risk, pubertal timing, and the sociocultural experience of gender contribute to neural changes underlying mood and anxiety symptoms. Therefore, in answer to the question posed by the mother at the beginning of this commentary, you could reply that her daughter is at a 2:1 increased risk for depression compared to her brother because of a combination of factors, including reproductive hormones, amygdala and salience network function, earlier timing of brain development, and social challenges specific to adolescent girls (Figure 1). Future research will inform us about the critical points in development at which we could intervene to

prevent progression to psychopathology. With such research, exciting opportunities exist for developing sex- and gender-specific dimensional risk phenotypes that can be used early in development to aid in identification of and intervention for individuals who are at risk for psychologic distress and potentially prevent subsequent disease.

Acknowledgments

Disclosures

This work was supported by and produced in collaboration with the National Neuroscience Curriculum Initiative. The National Neuroscience Curriculum Initiative receives support from the National Institutes of Health (Grant Nos. R25 MH10107602S1 and R25 MH086466 07S1).

We thank Drs. David Ross and Melissa Arbuckle for their contributions as National Neuroscience Curriculum Initiative editors.

Dr. Eckstrand reports no biomedical financial interests or potential conflicts of interest. Dr. Travis reports no biomedical financial interests or potential conflicts of interest. He is part of the National Neuroscience Curriculum Initiative, which receives support from the National Institutes of Health (Grant Nos. R25 MH10107602S1 and R25 MH086466 07S1). Dr. Forbes reports no biomedical financial interests or potential conflicts of interest. She receives grant support from the National Institute of Mental Health (Grant Nos. R01 MH104418, R01 MH093605, and R01 MH103230), and a National Alliance for Research on Schizophrenia and Depression Independent Investigator Award. Dr. Phillips is a consultant for Roche Pharmaceuticals, and she has received grant support from the National Institute of Mental Health (Grant Nos. MH0739053, MH060952, MH059929, MH100041, MH106435, and MH108421).

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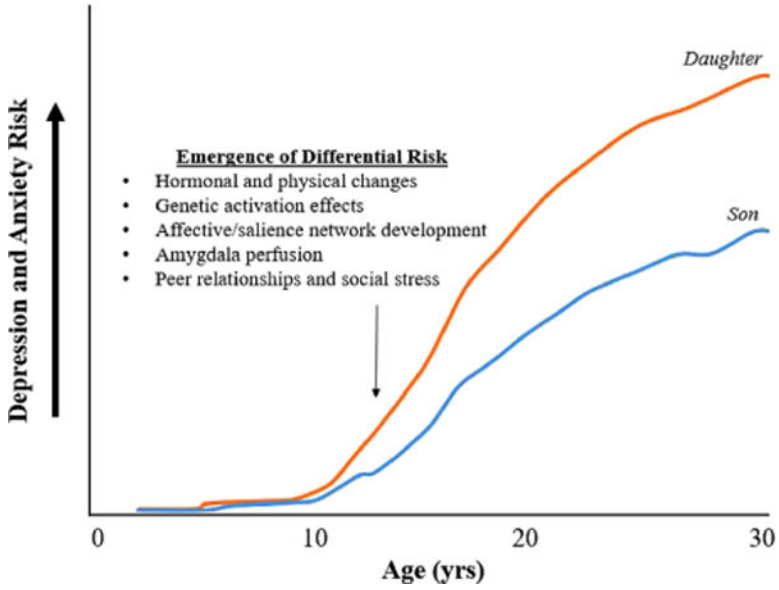

Figure 1.
Development of sex differences in depression and anxiety risk in adolescence.