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M. Altemus

N. Sarvaiya
Northwell Health

C. N. Epperson

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Sex differences in anxiety and depression clinical perspectives

Margaret Altemus^{a,b,*}, Nilofar Sarvaiya^c, and C. Neill Epperson^{d,e,f}

^aDepartment of Psychiatry, Weill Medical College, Cornell University, New York, NY, United States

^bDepartment of Complementary and Integrative Medicine, Weill Medical College, Cornell University, New York, NY, United States

^cNorth Shore-LIJ School of Medicine, Zucker-Hillside Hospital, Glen Oaks, NY, United States

^dDepartment of Psychiatry, Penn Center for Women's Behavioral Wellness, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, United States

^eDepartment of Obstetrics and Gynecology, Penn Center for Women's Behavioral Wellness, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, United States

^fPenn Center for the Study of Sex and Gender in Behavioral Health, University of Pennsylvania, United States

Abstract

Sex differences are prominent in mood and anxiety disorders and may provide a window into mechanisms of onset and maintenance of affective disturbances in both men and women. With the plethora of sex differences in brain structure, function, and stress responsivity, as well as differences in exposure to reproductive hormones, social expectations and experiences, the challenge is to understand which sex differences are relevant to affective illness. This review will focus on clinical aspects of sex differences in affective disorders including the emergence of sex differences across developmental stages and the impact of reproductive events. Biological, cultural, and experiential factors that may underlie sex differences in the phenomenology of mood and anxiety disorders are discussed.

Keywords

Depression; Anxiety; Sex difference; Development; Puberty; Hormones

1. Introduction

The onset of anxiety and depressive disorders peaks during adolescence and early adulthood, with females being at significantly greater risk than males. Women have twice the lifetime rates of depression and most anxiety disorders (Kessler et al., 1994, 1995; Weissman et al., 1994, 1996; Gater et al., 1998). The exceptions in term of sex ratio are obsessive-compulsive disorder and bipolar disorder, which have similar prevalence in men and women.

*Corresponding author. Address: Box 244, 1300 York Avenue, New York, NY 10065, United States. Fax: +1 212 746 3870. ; Email: maltemus@med.cornell.edu (M. Altemus)

However, even for these disorders, men and women have differences in disease presentation and course. In addition to higher rates of affective disorders that meet full diagnostic criteria, subclinical anxiety and depression symptoms are also more common in women (Nolen-Hoeksema et al., 1999; Hankin, 2009).

Understanding the biological and cultural underpinnings of sex differences in affective disorders is likely to be a useful window into mechanisms of illness in both men and women (Rutter et al., 2003). Sex differences in brain structure and function are abundant and fluctuate across development (Courchesne et al., 2000; Lampl and Jeanty, 2003; Patton et al., 2004; Lenroot et al., 2007; Raznahana et al., 2013; Ingahalikar et al., 2014). The challenge is to discern which sex differences in brain are relevant to sex differences in the epidemiology, phenomenology, and pathophysiology of affective disorders (DeVries and Sodersten, 2009). Some sex differences that promote reproductive success also likely increase vulnerability of women to mood and anxiety disorders. For example, adaptive behavioral differences in terms of childrearing seem to include, in females, superior social cognition and capacity for attunement with others, important for cognitive and social development of offspring (Halpern, 2007; Gur et al., 2012; Thompson and Voyer, 2014). However, these sex differences are also thought to result in women experiencing more sensitivity to rejection, criticism and separation, key features of depression and anxiety disorders (Cyranowski et al., 2000; Taylor et al., 2000; Zahn-Waxler et al., 2008; Martel, 2013). It is important to recognize that sex differences in behaviors and coping styles are not absolute, only more common in one sex than the other. In most instances, the magnitude of these sex differences are small. Although environmental influences, particularly cultural gender stereotypes, contribute to sex differences in human behavior and risk for psychiatric disorders, it is difficult to disentangle to what degree sex-specific cultural stereotypes are based on biologically determined sex-specific traits (Carter, 2011). Moreover, sex differences in life experiences and cultural expectations in turn may alter gene expression and contribute to development of sex differences in brain and physiology throughout the lifespan (Curley et al., 2011; Springer et al., 2012). For these reasons, we do not distinguish between sex and gender differences in this review.

In addition, the fluctuations in gonadal steroids and HPA axis regulation across the menstrual cycle and pregnancy are necessary for conception and gestation, but also expose women to more intense perturbation of gonadal steroid and glucocorticoid responsive brain systems. It is important to note that there are large individual differences in the activational effects of reproductive hormones on behavior. Although almost all women undergo the hormonal fluctuations related to menstruation, pregnancy and menopause, only a small minority of women (3–5%) experience the intense perimenstrual negative affect that occurs in women with premenstrual dysphoric disorder (Epperson et al., 2012) and similarly small subgroups of women experience perimenopausal or postpartum major depression (Gaynes et al., 2005; Freeman et al., 2014). The bulk of research indicates that these subgroups of women experience typical levels of reproductive hormone changes, but a sub-optimal central nervous system response that leads to negative affect and maladaptive behaviors (Schmidt et al., 1998; Bloch et al., 2000).

After a brief discussion of developmental events that have impact across mood and anxiety disorders, this review will summarize sex differences in the epidemiology, phenomenology and course of specific affective disorders across the lifespan, with a particular focus on periods of dynamic hormonal flux including puberty, pregnancy and reproductive senescence. Behavioral animal models are included where appropriate to illustrate potential biological mechanisms for sex differences in affective illness.

2. Developmental considerations

Biologically-determined sex differences can arise from effects of sex chromosome genes (Arnold et al., 2012; Lee and Harley, 2012; Raznahan et al., 2013; Seney et al., 2013), organizational effects of gonadal steroid exposure during development, and activational effects of reproductive hormone exposure throughout the lifespan (Arnold, 2009; McCarthy et al., 2012). In addition, recent animal studies suggest that maternal and paternal stress that occurs even prior to conception can have differential effects in male and female offspring on depression and anxiety related behaviors and stress-response regulation (Dietz et al., 2011; Zaidan et al., 2013).

2.1. Prenatal

In humans, exposure to fetal sex hormones starts at gestational week 7, at which point the male fetus begins to produce testosterone resulting in differentiation of the male genitalia and sex differences in the brain and other tissues. Testosterone levels peak in the fetal serum between weeks 12 and 18 of pregnancy (Finegan et al., 1989). At the end of pregnancy, when the level of estrogen-binding alpha-fetoprotein decline, the fetus has greater exposure to estrogens from the placenta, which inhibits the hypothalamic-pituitary gonadal axis of both males and females. Loss of this inhibition once the child is born causes a peak in testosterone in boys and a peak in estrogens in girls (Quigley, 2002). At birth the testosterone levels of the male fetus are ten times higher than those of females (DeZegher et al., 1992). This second testosterone surge in males persists for the first 3 months after birth, but less is known about the developmental effects of this postnatal surge.

The prenatal sex difference in androgen exposures appears to have behavioral significance. Lower amniotic fluid testosterone levels at mid gestation (weeks 13–20) was associated with a negative response bias and less response to rewarding stimuli during a functional magnetic resonance imaging (fMRI) task among boys studied between 8 and 11 years of age (Lombardo et al., 2012). As negative response bias to affective tasks is a common finding in individuals with major depression (Jaworska et al., 2014); the relatively greater levels of androgen exposures in utero in males may contribute to relative protection against major depression later in life.

Some studies of maternal psychosocial stress or anxiety during gestation indicate that, compared to females, male offspring expressed to stress or anxiety in utero are more likely to exhibit externalizing behaviors during childhood. (Martin et al., 1999; deBruijn et al., 2009). Unfortunately, these studies have not extended to children post-puberty to determine the impact of pre-natal maternal stress on risk for affective disorders in females, which emerges in adolescence. With this said, longitudinal cohort studies suggest that low birth

weight and being small for gestational age, evidence of a sub-optimal in utero milieu and fetal stress, lead to relatively greater risk of depression in adolescent (Patton et al., 2004; Costello et al., 2007; vanLieshout and Boylan, 2010), and adult (Rice et al., 2007) but not pre-adolescent (Costello et al., 2007; vanLieshout and Boylan, 2010) females. In addition, elevated levels of maternal depression and cortisol during pregnancy (Buss et al., 2012; Sandman et al., 2013) and elevated milk cortisol levels during lactation (Grey et al., 2012) have been associated with more fearful and reactive behavior in female infants and children compared to male offspring.

The timing and nature of stress during pregnancy may influence its impact on sex differences in mood regulation later in life. Maternal emotional stress during the first trimester has been linked to internalizing symptoms and negative emotionality in boys (Martin et al., 1999; deBruijn et al., 2009), while maternal stress in later trimesters has been linked to increased risk of internalizing symptoms in girls during childhood (deBruijn et al., 2009) and adolescence (vandenBergh et al., 2008). This pattern of greater male vulnerability to depressogenic effects of prenatal stress in the first trimester is supported by a recent animal model. Chronic variable maternal stress early in pregnancy produced a depressive pattern of hormonal and behavioral stress responses, and brain CRH and glucocorticoid gene expression only in male offspring. In this same study, only male placentas showed changes in expression of placental growth genes in response to the stress (Mueller and Bale, 2011).

In contrast, childhood-onset non-affective neuropsychiatric disorders with prominent neurological and cognitive symptoms, including autism, Tourette's Syndrome, childhood-onset OCD and attention deficit hyperactivity disorder are more common in boys. Prenatal stress increases risk of these disorders (Mottagh et al., 2010; Schaafsma and Pfaff, 2014), suggesting that in utero, development of motor, attention and social communication systems are more vulnerable to stress in males than females. Similarly, fetal growth restriction and preterm birth are associated with more neurologic deficits in males than females (Halpern, 2007; Gur et al., 2012). Support for the notion that prenatal androgen exposure plays a role in the sex differential in risk for these conditions comes from the observation that girls with tic disorders have more gender dysphoria, masculine play preferences, and masculine performance style on spatial tasks (Alexander and Peterson, 2004), similar to findings in women with greater prenatal exposure to androgens. (Hines, 2006)

2.2. Postnatal

Environmental exposures that vary in type and frequency between males and females also are likely to contribute to sex differences in affective disorders. Childhood sexual abuse (before 18 years of age) which occurs in as many as 14.5% of women and 7.2% of men in the United States (Gorey and Leslie, 1997) has been linked to both depression and anxiety disorders and to inflammatory illnesses during adolescence and adulthood (Felitti et al., 1998; Dube et al., 2009; DeBellis et al., 2011). Childhood sexual abuse is also strongly associated with experiencing multiple other forms of adverse childhood events (Dong et al., 2003). The number of adverse childhood experiences has a graded impact on adult depression and other common medical conditions associated with increased risk of depression including heart disease, obesity, type II diabetes, and teen pregnancy, setting in

bold relief the impact of sex differences in early life exposures on long-term physical and mental health (Dube et al., 2005; Edwards et al., 2005).

The impact of sexual abuse on children is modulated by many factors, including age, parental functioning, social support, severity and duration of abuse, use of force, socioeconomic status, perinatal insults, family history of affective illness, and victim's relationship to the perpetrator. Childhood sexual abuse has been linked to dysregulation of biological stress response systems and alterations in brain development, which may mediate the association with affective disorders (DeBellis et al., 2011). It is difficult to differentiate the effects of sexual abuse from neglect, physical abuse, family dysfunction, and other adverse experiences, that occur as commonly in boys as in girls (CDC, 2010). However, 15.2% of women report having experienced four or more types of adverse childhood events (abuse, neglect or household dysfunction) compared to 9.2% of males, while 38% of males report having had no adverse childhood events compared to 34% of females (CDC, 2010). These data suggest that early adversity may differentially impact women compared to men based upon the graded effects of these environmental exposures.

Another important sex difference which emerges in childhood is coping style. Sex-linked differences in social support are apparent well before puberty, as evident in the language in single-sex peer groups (Maltz and Borker, 1983; Maccoby, 1990). Boys are more likely to command, threaten, and interrupt one another within same-sex group interactions. In contrast, girls are more likely to express agreement, to acknowledge another's point, and to pause to let each other speak. Other studies have found that in middle childhood boys develop more avoidant coping and girls more often demonstrate preoccupied and anxious coping in personal relationships (Carter, 2011; Gluck et al., 2014). Adolescent girls express more distress associated with friendships and more negative life events than boys (Ge et al., 1994; Hankin et al., 2007). This difference in coping style persists into adulthood (Deacon et al., 2003). In general, under conditions of perceived threat, men are more likely to escape or cope by taking action, and women are more likely to express affiliative behavior and seek support from others (Taylor et al., 2000). The magnitude of the sex difference in coping style is smaller in East Asian and African samples (deBrujin et al., 2009), providing evidence that this sex difference is determined, at least in part, by culture.

In addition to gender differences in exposures to environmental stressors, women have marked and characteristic fluctuations in exposure to reproductive hormones and peptides during the menstrual cycle, pregnancy and lactation, while men are exposed to relatively stable gonadal hormones during this period. Estrogen levels rise 5–8-fold during the 2 week follicular phase of the menstrual cycle, reaching a peak at ovulation. Androgen hormones also rise in women for a few days surrounding ovulation. Starting at ovulation, the corpus luteum, a remnant of the dominant ovarian follicle, produces progesterone, so that circulating levels rise over 20-fold over the following 12 days, and, if pregnancy does not occur, decline abruptly to basal levels during the last few days before onset of menses. If pregnancy occurs, estrogen and progesterone and numerous other hormones and peptides, including prolactin and oxytocin, are produced by the placenta and levels of these placental hormones rise exponentially during pregnancy, then fall precipitously at delivery. During lactation, oxytocin and prolactin production are maintained. Of note both pregnancy and

lactation suppress hypothalamic–pituitary adrenal axis and autonomic responses to stress (Matthews and Rodin, 1992; Altemus et al., 1995; Entringer et al., 2010). This suppression state may have been the set point for anxiety and stress responsivity in women. The relatively recent development of women spending much of their adult life neither pregnant nor lactating, may contribute to the increased rates of anxiety and depression in women, particularly in the context of repeated menstrual cycling and menopause which was relatively uncommon among women hundreds of years ago. In addition, pregnancy and infant care can be more stressful for women in terms of sleep deprivation, time demands, family adjustment and financial strain.

There are also sex differences in behaviors that expose individuals to increased risk for depression, mania or anxiety. For example, men are much more prone to abuse anabolic steroids which can induce both hypomania and depression (Martin et al., 1999). On the other hand, women are much more prone to eating disorders, with associated hypothyroidism, which can increase risk of depression. Medical disorders that increase risk of depression or the clinical features of depression, may also differentially affect men and women. For example, the most prevalent autoimmune disorder is Hashimoto's disease, which is twice as common in women and causes hyper and hypothyroidism. These thyroid conditions both substantially increase the risk for major depression, and hyperthyroidism also increases the risk for panic and other anxiety disorders. Substance-induced and medically-induced cases of anxiety and depression disorders are a relatively small proportion of the total of individuals with affective illness. Although these subtypes are important to recognize and require specific treatment of the exogenous or medical triggers, they do not account for the increased prevalence of affective illness in women.

Coming to the aging end of the lifespan, it is important to consider the impact of reproductive senescence on risk for affective disorders. Although males do not have menstrual cycle or pregnancy-related fluctuations in reproductive hormone, after age 20, there is a steady, and gradual decline in adrenal and gonadal androgen hormone levels. Women also have a gradual reduction in adrenal androgen hormones, but also experience a marked variability of gonadal steroid hormones in perimenopause. In the 7th and 8th decades of life, both men and women are more likely to experience disabling medical illnesses, pain, physical frailty, brain microvascular events and cognitive impairment, all of which increase risk of anxiety and depression.

3. Sex differences in mood disorders

3.1. Major depression

Prior to puberty, depression is difficult to diagnose, but estimated prevalence of 5% and the symptom profile are similar in boys and girls. Longitudinal studies have identified Tanner Stage III, the start of ovarian cycling, when estrogen levels rise significantly, as the onset of increased rates of major depression in girls (Angold et al., 1998). The increased risk of depression was evident only in girls with a family history of depression, suggesting that onset of puberty may activate a genetic vulnerability in females. Adolescent girls experience more objective and subjective stressors than boys, and this sex difference in stress exposure, particularly interpersonal stress, has been shown to partially mediate the increased

prevalence of depression in girls after puberty (Ge et al., 1994; Hankin et al., 2007). After puberty, females experience major depression at roughly twice the rate of males until late middle age when women transition to menopause.

With respect to sex differences in symptom profile, recent findings from the Sequenced Treatment Alternatives To Relieve Depression (STAR-D) study indicate that women seeking depression treatment report greater symptom severity, and more increased appetite, weight, hypersomnia, interpersonal sensitivity and gastrointestinal symptoms. Women are more likely than men to have a comorbid anxiety disorder, bulimia or somatoform disorder and to report more past suicide attempts. Men are more likely to report comorbid alcohol and substance abuse (Marcus et al., 2008). Other studies support the observation that women are more likely to experience disturbances of sleep, appetite and energy during a depression (Silverstein, 1999), as well as more likely to experience “atypical” depression, with hypersomnia and weight gain (Young et al., 1990; Angst et al., 2002; Blanco et al., 2012). Atypical depression is also associated with younger age of onset, more comorbidity with social anxiety and specific phobia and more severity, disability and suicide attempts. Of note, pre-menstrual dysphoric disorder, discussed below, is also characterized by hypersomnia and increased appetite. Although women make more suicide attempts, men are more likely to make a lethal attempt (Rudmin et al., 2003). Several studies have noted better responses to serotonin reuptake inhibiting antidepressants (SSRIs) in women and better response to tricyclic antidepressants in men and older women (Kornstein et al., 2000; Khan et al., 2005), suggesting that inhibition of serotonin reuptake may mitigate the mood-stabilizing effects of changes in gonadal steroids. Alternatively, the greater efficacy of SSRIs in reproductive aged women may be due to SSRI induction of 3-alpha reductase (Uzunov et al., 1996; Pinna et al., 2009), the enzyme producing the anxiolytic metabolites allopregnanolone (3-alpha,5-alpha metabolite of progesterone) and the 3 alpha, metabolites of androstenedione and dihydrotestosterone (Porcu et al., 2009).

Because there are such clear sex differences in hypothalamic–pituitary–adrenal (HPA) axis regulation in rodents, and HPA axis regulation is often disturbed during depressive episodes, much attention has been focused on a causal role for sex differences in the HPA axis in generating sex differences in vulnerability to depression. However, in humans, despite substantial effort, there is little evidence to support this hypothesis. Sex differences in HPA axis regulation are much smaller and less consistent in humans than rodents (Kudielka and Kirschbaum, 2005; Panagiotakopoulos and Neigh, 2014) and most anxiety disorders do not show any consistent perturbation of the HPA axis. It remains to be seen whether the sex differences in central CRH and noradrenergic regulation observed in rodents (Bangasser and Valentino, 2014) also are present in humans and to what degree they may contribute to increased rates of depression and anxiety disorders in women.

More than half of women with major depression experience increased severity of depression symptoms in the premenstrual phase of the menstrual cycle, even when antidepressant medication is effective during the remainder of the cycle. Premenstrual exacerbation of depression has been linked in several studies to shorter time to relapse (Haley et al., 2013).

It is arguable whether there is an increased risk of major depression in relation to pregnancy and childbirth, although the Diagnostic and Statistic Manual for Mental Disorders Fifth Edition (DSM-5) (American Psychiatric Association, 2013) allows for the continued use of the peripartum onset specifier for occurrence of major depression in the third trimester and up to 4 weeks after childbirth. The heterogeneity of depression and of groups studied may obscure the true relationship between major depression and perinatal hormonal fluctuations. Of women who have major depression postpartum, approximately one quarter have chronic depression, one third have depression that onset during pregnancy and only a little more than one third have actual postpartum onset of depression (Wisner et al., 2013). Compared to women with postpartum onset of major depression, women who have onset of major depression during pregnancy are more likely to have a prior history of depression, and history of typical risk factors for depression including abuse and low social support (Stowe et al., 2005; Altemus et al., 2013). Findings from a hormonal challenge study conducted in healthy parturient women with no history of postnatal depression and a comparison group with a history of postpartum depression suggests that with exposure to and withdrawal of pregnancy levels of estradiol and progesterone, there are subset of women who are particularly vulnerable to develop depression (Bloch et al., 2000). Whether these women are the same women as those who demonstrate depressed mood when exposed to menstrual cycle levels of these hormones or when they undergo the menopause transition has not been fully elucidated but is suspected.

During the menopause transition, the risk for relapse of major depression is 4–6-fold greater for women who have a history of major depression and 2–3-fold for those women with no history of major depression during the childbearing years. Importantly, the risk for major depression appears to decline in the years post-menopause such that there are no longer sex differences in risks for major depression (Cohen et al., 2006; Freeman et al., 2014). Women do experience an age-independent decline in immediate and delayed verbal recall during the menopause transition suggesting that changes in reproductive function impact cognition in addition to mood in women (Epperson et al., 2013a). Findings from a large community cohort followed for 14 years from the pre to post-menopause indicates that exposure to two or more adverse childhood events (before age 18) increases the risk of first onset of major depression in the perimenopause by 2-fold and recurrence of major depression 5-fold (Epperson et al., 2013b). As childhood adversity is a known risk factor for affective disorders across the lifespan, it is fascinating that for some exposed women the risk for major depression was not unmasked until they experienced the hormonal fluctuations of the perimenopause. The most recent report from this cohort, provides further evidence that risk for clinically meaningful depression declines in women after the menopause transition has been completed (Freeman et al., 2014). Prevalence data is sparse for late life affective disorders, but rates in men and women appear to be more similar after menopause (Quigley, 2002). The importance of hormonal fluctuations to the pathogenesis and treatment of depression during the menopause transition is suggested by the relative increased risk in major depression prior to compared to after the last menstrual period. In addition, two randomized clinical trials (Schmidt et al., 2000; Soares et al., 2001) indicate that typical hormone therapy doses of estradiol (50 or 100 µg/d) are significantly more effective than

placebo in treating major depression with perimenopause onset, a finding that is lacking for major depression during the postmenopause (Morrison et al., 2004).

3.2. Bipolar disorder

Bipolar disorders are mood disorders that include episodes of mood elevation or mania, often accompanied by additional episodes of depression or mixed states. The bipolar I disorder diagnosis requires an episode of full mania, involving hospitalization or severe functional impairment, and the Bipolar II diagnosis requires episodes of hypomania, which are less severe. The lifetime prevalence of bipolar I disorder in the National Comorbidity Survey Replication was 0.8% in men and 1.1% in women and the lifetime prevalence of bipolar II disorder is 0.9% in men and 1.3% in women (Merikangas et al., 2007). Prevalence rates of bipolar II in adolescents was higher at 3–4% in recent studies, likely because some of these individuals will convert to bipolar I or other diagnoses over time (Merikangas and Lamers, 2012). Although bipolar I disorder occurs equally as often in males and females, women comprise 70% of the cases of rapid cycling bipolar disorder (Liebenluft, 2000). Women with bipolar I or II disorder are more likely to experience depressive episodes and depression symptoms, than men with these disorders (Angst, 1978, Kessler et al., 1997).

There is a remarkable increased risk of a mania and psychosis during the first few weeks postpartum, with an incidence of 0.1–0.2 (Stewart et al., 1991). The vast majority of these episodes are a first episode or recurrence of bipolar I disorder (Munk-Olsen et al., 2012; Sharma and Pope, 2012). However, recent observations suggest that some women may experience these episodes only postpartum, and are not otherwise at risk of recurrence. Women with postpartum manic episodes often experience more disorganization, disturbed sensorium, bizarre behavior, and sense of persecution than seen in typical manic episodes (Brockington et al., 1981; Wisner et al., 1994). During postpartum psychotic episodes, women are at risk of infanticide due to delusions that incorporate the infant. Childbirth also seems to be a trigger for a hypomanic episodes, which can occur in 10–20% of women and in the early postpartum period (Heron et al., 2009). Postpartum hypomania may foreshadow the onset of a depression that occurs in about half of females who experience postpartum mood elevation (Sharma and Pope, 2012). In addition, women who experience postpartum depression are at increased risk to develop bipolar disorder in long-term follow-up (Munk-Olsen et al., 2012). There has been relatively little study of the effect of the menstrual cycle on bipolar symptoms, but preliminary evidence suggests that women with bipolar disorder have increased rates of premenstrual dysphoric disorder and approximately 50% of women with bipolar disorder report mood changes tied to their menstrual cycle, including in some cases, manic symptoms at ovulation and premenstrually (Teatro et al., 2014).

3.3. Seasonal affective disorder

Seasonal affective disorder is characterized by mood disturbances that typically occur in the autumn and winter with remission in the spring or summer. Seasonal changes in patterns of depression are quite common, with an overall population prevalence of 3–10%, and a female to male ratio of 2:1. Seasonal affective disorder is especially common in women during reproductive years from puberty until the sixth decade of life. Available studies reveal little to no sex differences in the clinical course of seasonal affective disorder or response to light

therapy. However, there is evidence that on self-report scales, women report more carbohydrate cravings, more weight gain, and more hours of sleep per night in the winter (Lucht and Kasper, 1999).

3.4. Premenstrual dysphoric disorder (PMDD)

PMDD is a constellation of premenstrual mood and physical symptoms severe enough to significantly impair functioning. Under current diagnostic criteria (American Psychiatric Association, 2013), PMDD affects 3–8% of reproductive-aged women. PMDD is distinguished from other affective disorders by emergence of symptoms only in the luteal phase of the menstrual cycle, and the prominence of irritability and the physical symptoms of fluid retention, increased appetite and fatigue. The major hormonal change in the luteal phase is secretion of progesterone by the corpus luteum, which begins at ovulation and falls to baseline during the last few days of the luteal phase, triggering the onset of menses. Women with PMDD do not have abnormal levels of estrogen, progesterone, or other gonadal steroids across the cycle (Rubinow et al., 1988), but instead are more reactive to luteal phase progesterone in terms of both mood and physical symptoms (Schmidt et al., 1998). Experimental and treatment studies have shown that PMDD symptoms are relieved by elimination of ovulation (Schmidt et al., 1998). However, progesterone receptor blockade does not relieve symptoms (Schmidt et al., 1991), indicating that symptoms are generated by a metabolite of progesterone, or progesterone acting through membrane effects or other non-classical receptor mechanisms. There is preliminary evidence from retrospective twin and family studies that risk for PMDD is heritable (Wilson et al., 1991; Condon, 1993) and may be distinct from genetic risk for anxiety and depression (Kendler et al., 1992). Retrospective reports of women who meet full diagnostic criteria for PMDD indicate high comorbidity between major depression, bipolar disorder, seasonal affective disorder and panic disorder among adult women who meet full diagnostic criteria for PMDD (Kim et al., 2011), but this indication of shared vulnerability for PMDD and other affective disorders needs to be confirmed by prospective studies. It also remains to be determined whether PMDD is associated with an increased risk of depression during pregnancy or postpartum, when hormonal changes are much larger, more numerous, and more sustained. Frequency of ovulatory cycles is relatively low at onset of puberty and increases to 90% over the course of adolescence, in the absences of eating disorders.

Although to date, there have been no genetic polymorphisms or other genetic variants linked to premenstrual or perinatal mood disorders, a recent female rodent model suggests the Val66Met BDNF polymorphism as a risk factor for depression and premenstrual mood disorder in women. In a female rodent model, using mice transfected with the human Vall66Met BDNF polymorphism, only animals homozygous for the human depression risk allele, which reduces BDNF availability, showed fluctuation in anxiety behaviors across the estrus cycle (Bath et al., 2012).

Cross-sectional surveys of adolescent girls suggest that PMDD and distressing premenstrual symptoms, which do not meet threshold for PMDD occur at roughly the same rate in adolescent girls as in adult women (3–6% for PMDD and up to 20% for premenstrual syndrome or subthreshold PMDD) (Epperson et al., 2012). The findings are remarkably

similar whether one assesses girls growing up in Asia, Africa, Canada or Slovakia or different areas of the United States (Ogebe et al., 2011; Steiner et al., 2011; Yang et al., 2012).

4. Sex differences: anxiety disorders

In contrast to major depression which has an increased prevalence in girls beginning in mid-puberty, the increased risk of anxiety and anxiety disorders in girls begins in middle childhood (Lewinsohn et al., 1998). In addition, the increased tendency to ruminate, a risk factor for major depression, emerges in girls by age 9, also prior to puberty (Nolen-Hoeksema and Girgus, 1994).

4.1. Post-traumatic stress disorder (PTSD)

There is a wide variation in the response of individuals to trauma. It is typical to have increased arousal, insomnia, and even nightmares for days or weeks following an acute or repeated trauma. But when hyperarousal, intrusive memories, nightmares, irritability, vigilance and avoidance persist and impair functioning, individuals meet diagnostic criteria for PTSD. The diagnosis of PTSD requires that a person experiences or witnesses an intense, overwhelming, real or threatened traumatic event, reacts with fear or disorganized behavior and has three clusters of categorical symptoms for at least 1 month: (a) intrusive re-experiencing of the trauma (s), (b) persistent avoidance of stimuli associated with the trauma, and (c) persistent symptoms of increased physiological arousal (American Psychiatric Association, 2013). To date, there is no evidence of differences in symptom presentation between men and women.

The lifetime prevalence of PTSD in the United States is estimated at 5.0% for men and 10.4% for women based on the National Comorbidity Survey (Kessler et al., 1995). Other studies also consistently find that PTSD is more common in women than men (Narrow et al., 2002; Tolin and Foa, 2006; Roberts et al., 2011). However, there is much debate about the source of this sex difference. Proposed determinants of the sex difference include increased rates of childhood trauma in women, increased reactivity of women to some types of trauma, increased rates of re-victimization in women, increased symptom reporting in women, and biological sex differences in both stress response physiology and neural organization. It is also possible that there is sex difference in propensity to recall trauma or to remember events as traumatic (Freedman et al., 2002; Dube et al., 2005). Several studies indicate that pregnancy complications or loss can lead to full (9%) or partial PTSD (18%) with clinically significant distress, particularly during future pregnancies (Forray et al., 2009).

There is disagreement as to whether men or women have greater exposure to trauma (Robin et al., 1997; Breslau et al., 1999; CDC, 2010) and sex itself is relatively weak predictor of trauma exposure (Brewin et al., 2000). Women compared to men, however, are 10 times more likely experience sexual assault (Kessler et al., 1995) and sexual assault has been shown to be a major contributor to the sex difference in PTSD prevalence (Stein et al., 2000). In the military, among troops deployed overseas, sexual assault is over 15 times more common in women, and military sexual assault has a greater likelihood to result in PTSD in women compared to men (Kimerling et al., 2010).

Two recent meta-analyses found that when controlling for type of trauma, women do seem to be more likely than men to develop PTSD in response to a number of stressors including combat (Crum-Cianflone and Jacoson, 2014), refugee status, accidents, witnessing death and illness/injury (Freedman et al., 2002; Tolin and Foa, 2006). Of note, there did not seem to be a sex difference in response to non-sexual abuse or neglect, or non-military sexual assault in adulthood (Tolin and Foa, 2006). However, there are few prospective studies and few studies control for resiliency factors such as age, education, social support, prior trauma, severity of trauma, psychiatric history, and other life stresses. Resilience factors also seem to differ by sex. Among army personnel deployed to combat settings, risk of PTSD was attenuated by supportive personal relationships in women but not men (Maguen et al., 2012).

There is some suggestion of sex differences in PTSD biomarkers. Several studies have noted that female children and adults are less likely to have reduced hippocampal volume associated with trauma or PTSD (Debellis and Keshavan, 2003; Samplin et al., 2013) but this finding was not evident in a recent meta-analysis (Woon and Hedges, 2011). In addition, blood levels of PACAP, a neuropeptide involved in coordinating the brain's response to stress and a polymorphism in the gene that encodes PACAP's receptor PAC1, are both associated with increased risk for PTSD in women, but not in men (Ressler et al., 2011). The receptor gene risk variant is located within an estrogen response element, suggesting that the association with PTSD in women could be stronger due to greater exposure to circulating estrogen.

Finally, a few experimental studies have demonstrated increased vulnerability to intrusive negative memories, when traumatic material is presented in the early luteal phase of the menstrual cycle compared to the follicular or late luteal phase (Soni et al., 2013).

4.2. Obsessive–compulsive disorder (OCD)

The 12-month prevalence of OCD in the United States is 1.2% and lifetime rates are 2–3% (Kessler et al., 2005; Ruscio et al., 2010), with a similar prevalence internationally (Weissman et al., 1994). Females are affected at the same rates as males in adulthood, but 70% of children with OCD are male (Weissman et al., 1994; Ruscio et al., 2010). Boys with OCD and adult men with childhood onset OCD are more likely to have comorbid tics, and attention deficit disorders (Leckman et al., 2010; Ruscio et al., 2010). Clinic-based studies suggest that childhood onset OCD may be a distinct subtype of OCD, more common in males, and with greater familial risk (Geller et al., 1998; Hemmings et al., 2004). However, a large adult population study demonstrated that risk of OCD in relatives was proportional to degree of familial relationship, there was no impact of the sex of the proband or relative (Mataix-Cols et al., 2013), suggesting that there is no sex difference in the heritability or familial risk for OCD. In terms of symptomatology, women are more likely to have contamination obsessions, cleaning compulsions and obsessions about harming others and checking, while men are more likely to have intrusive sexual and religious obsessions and symmetry and ordering compulsions. Also, men with OCD have more social phobia and are less like to marry (Torresan et al., 2012).

OCD symptoms are unusually common in postpartum depression, occurring in up to 35% of women with postpartum onset depression (Wisner et al., 1999; Altemus et al., 2013). In a

survey of adult women with OCD, 32% reported that their main symptoms began either during pregnancy or the early postnatal period. Those women who reported onset of OCD or worsening of their ongoing OCD symptoms in the perinatal period, were also more likely to indicate that their symptoms worsened premenstrually (Forray et al., 2010). Although these findings await confirmation using prospective assessments, they suggest that the hormonal milieu associated with pregnancy, postpartum and the luteal phase of the menstrual cycle may trigger or exacerbate OCD symptoms in “hormonally sensitive” women.

4.3. Panic disorder

Patients with panic disorder often suffer from sudden, 10–20 min bursts of fear, hypervigilance, and distressing physical symptoms such as tachycardia, tachypnea, chest pain, and nausea. Panic attacks occur in association with many anxiety disorders, but panic disorder is distinguished by a fear of recurrent panic attacks to the point that functioning is impaired (American Psychiatric Association, 2013). Panic attacks are often accompanied by agoraphobia, an avoidance of places or situations where panic attacks could occur. The prevalence of panic disorder and agoraphobia is two to three times higher in women than in men (Kessler et al., 1994), with the sex difference in prevalence emerging in adolescence (Beesdo et al., 2009).

An important consideration in the sex-differences seen in panic disorder is a phenomenon called anxiety sensitivity, or the fear of anxiety related sensations. Many studies have found that females of all ages have greater anxiety sensitivity than males (Deacon et al., 2003; Bernstein et al., 2006). Women are more likely to describe a feeling of “shortness of breath”, “faintness”, and “feeling smothered” and tend to fear the physical symptoms of panic, whereas men more often fear the social consequences of anxiety. (Sheikh et al., 2002). A possible explanation for this finding is that women are more likely to receive positive reinforcement when expressing concerns about their symptoms that could encourage self-focused attention and more perceived physical discomfort.

The postpartum period has been identified as high risk for onset or relapse of panic disorder (Sholomskas et al., 1993; Klein, 1994), possibly due to the abrupt drop in progesterone and allopregnanolone levels after delivery, and the loss of the facilitating action of these hormones on GABAergic transmission. Of all of the anxiety disorders, panic disorder is particularly responsive to benzodiazepine treatment (Offidani et al., 2013). There is no evidence to date of a change in vulnerability to panic across the menstrual cycle or during perimenopause.

4.4. Generalized anxiety disorder

Generalized anxiety disorder is highly comorbid with major depression, and is characterized by constant, nonspecific, often irrational worry in daily life that can result in significant functional impairment (American Psychiatric Association, 2013). The lifetime prevalence of generalized anxiety disorder is higher in women 6.6% vs. 3.6% in men (Kessler et al., 1994), with the sex difference emerging in mid-adolescence (Beesdo et al., 2009). Though the mean age of onset, 32 years old, is similar in men and women, there are sex differences in the course and clinical presentation of generalized anxiety disorder. Women with generalized

anxiety disorder more frequently complain of somatic discomfort including fatigue, muscle tension, and autonomic, cardio-respiratory, and gastrointestinal symptoms than men. Men are more likely to report strained relationships with friends and family as a result of excessive worry. Among individuals with a chronic course of generalized anxiety, men are more likely to have co-morbid alcohol and substance abuse while women have higher rates of co-morbid mood and anxiety disorders (Vesga-Lopez et al., 2008).

4.5. Social anxiety disorder

Social anxiety disorder is a common psychiatric disorder characterized by the intense fear of being in social situations or being observed, which can lead to considerable distress and functional impairment in daily life. The lifetime prevalence of social anxiety disorder is higher in women at 5.7–15.5% compared to 4.2–11.1% in men (Kessler et al., 1994; Grant et al., 2005), with the sex difference in prevalence emerging prior to puberty (Beesdo et al., 2009). Sex differences have been noted in the likelihood of having particular clinical features of the disorder. Women are more likely to fear being interviewed, speaking to an authority figure, speaking up at meetings, eating and drinking in front of people, and taking important exams. Men with social anxiety disorder are more likely to fear dating and have a higher likelihood of being single, separated, or divorced. Of note, men often have co-morbid externalizing disorders such as antisocial personality disorder, pathological gambling, and substance abuse. Women, on the other hand, tend to have co-morbid internalizing disorders such as mood or other anxiety disorders. Women also report a higher number of social fears and a greater incidence of situational panic attacks (Xu et al., 2012). Women with social anxiety often experience symptom exacerbation premenstrually (van Veen et al., 2009), but little is known about the course of social anxiety during pregnancy or perimenopause.

In neuroimaging studies examining sex differences in responses to threatening social cues, such as angry facial expressions, women are consistently more sensitive to interpersonal threats and exhibit greater reactivity to social rejection when compared to men, and men were more reactive to achievement stress (Stroud et al., 2002; McClure et al., 2004).

4.6. Specific phobias

A specific phobia is defined as a persistent fear that is excessive or unreasonable and that is cued by the presence of a specific object or situation. Specific phobias are classified into five major types: animal (e.g., insects, snakes, dogs), natural environment (e.g., darkness, storms, heights), situational (e.g., enclosed spaces, elevators, flying), blood-injection-injury (BII) (e.g., seeing blood, receiving shots or injections), and other (e.g., choking, loud sounds, costumed characters) (American Psychiatric Association, 2013). Specific phobias have the earliest onset of all anxiety disorders and are more than 2-fold as prevalent in girls (Beesdo et al., 2009) and adult women (Kessler et al., 1994). Lifetime prevalence of specific phobia in adults have been reported as 6–12% in men and 12–27% in women (Kessler et al., 1994; Fredrikson et al., 1996; Stinson et al., 2007). Women have a higher proportion of animal phobias and environmental phobias compared to men. Height phobia is the most common type of specific phobia among men (3.3–6.3%), but the second or third most common type of SP among women (1.6–8.6%). Situational phobia, which has a later age of onset in early adulthood and has triggers more similar to panic disorder, also is more prevalent among

women (6.4–17.4%) than men (1.6–8.5%). Findings regarding the sex ratio of blood-injection-injury phobia have been more mixed (LeBeau et al., 2010). To date, there is no evidence of any effect of reproductive events on the onset or course of specific phobia. This observation, together with the childhood onset of phobias, suggest that the increased prevalence in women arises from other factors than activational effects of gonadal steroids.

5. Summary

Although there is higher prevalence of affective disorders in women and some sex differences in symptom pattern and course of illness, it is difficult to identify the biological and cultural factors that contribute to the generation of these sex differences. Mood and anxiety disorders are highly comorbid and have shared symptoms and familial risk (Angold et al., 1999; Kotov et al., 2011; Kravitz et al., 2014), suggesting that some of the same mechanisms are likely contributing to increased female vulnerability across this group of disorders. On the other hand, twin studies in adults suggest there are also specific genetic factors contributing to specific phobia, generalized anxiety disorder and panic disorder (Kendler et al., 1992). One theme that emerges from clinical observations is that the years between puberty and menopause are when rates of depression and only some anxiety disorders become higher in women. While girls demonstrate more internalizing coping styles, rumination and anxiety than boys, the sex difference in prevalence of major depression does not emerge until the onset of ovarian cycling and the sex difference in prevalence of generalized anxiety disorder and panic disorder also is not evident until adolescence. On the other hand, during childhood, girls have 2-fold higher rates of rates of separation anxiety, specific phobias and social phobia, pointing out mechanisms other than ovarian cycling contribute to increased rates of these anxiety disorders in women. These anxiety disorders are associated with the “atypical” subtype of major depression, which also has an earlier age of onset than non-“atypical” major depression.

Another important observation is that puberty, the menstrual cycle, pregnancy and menopause are triggers for onset, recurrence and exacerbation of affective disorders. But again, the brain systems and biological mechanisms, and psychological demands mediating the psychiatric effects of these reproductive events are not well understood. The hormonal milieu is quite different in the vulnerable periods of the luteal phase, postpartum and perimenopause, and we have little longitudinal data to determine whether the same or different women are most vulnerable to mood dysregulation during these distinct reproductive events. These reproductive events involve changes in multiple hormones and hormone metabolites, and then multiple downstream brain systems. Unfortunately, clinical studies have focused too narrowly on estrogen during puberty, postpartum and menopause, and too narrowly on serotonin premenstrually. Better understanding of how hormonal changes cause emergence of affective symptoms, and why some women are more vulnerable to affective illness during reproductive events should help to clarify neurobiological and cognitive processes that generate anxiety and depression.

Comparison of clinical features between men and women points to features such as rumination, more common in women; irritability, strikingly prominent in PMDD; and hypersomnia and hyperphagia, more common in depressed women and in PMDD, which

offer more focused areas for understanding the pathophysiology of symptom generation in women and possibly men as well. In addition, postpartum depression and mania offer the opportunity to study more homogenous subsamples of major depression and bipolar disorder, which also is likely to facilitate discovery of risk factors and pathophysiological mechanisms.

Strategies to clarify the mediators of sex differences in affective disorders include longitudinal observational studies across periods of hormonal change that incorporate neuroimaging, neuropsychological testing, and other biomarkers as well as clinical trials of psychological, pharmacologic and hormonal interventions targeting factors hypothesized to contribute to female vulnerability. In addition, identification of sex-specific and hormone responsive genetic risk factors has the potential to clarify mechanisms of vulnerability that could operate in both men and women. Finally, cross-cultural comparisons may be helpful in determining the contribution of social expectations and experiences to the higher female prevalence of depression and anxiety disorders,

In sum, study of sex differences in anxiety and depression has the potential to shed light on factors that contribute to resiliency as well as vulnerability, and to point to new ways to reduce risk and develop treatments for both men and women suffering from affective disorders.

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