Special Article

Psychopathology in Women and Men: Focus on Female Hormones

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Objective: *The goal of this overview is to examine male/female differences in psychopathology in light of the known effects of gonadal steroids, especially estradiol, on neural function.* *Method:* *The epidemiology of specific psychopathological syndromes is highlighted with respect to male/female differences and discussed against the backdrop of recent neuroendocrine findings.* *Results:* *A number of differences between the sexes in rates of illness and course of illness are documented, with Alzheimer's disease, schizophrenia, alcoholism, and mood and anxiety disorders each illustrating slightly different hormone-mediated risks and buffers.* *Conclusions:* *Estrogens are neuroprotective with respect to neuronal degeneration, growth, and susceptibility to toxins. The cyclic fluctuations of estrogens and progesterone enhance the response to stress, which confers susceptibility to depression and anxiety.*

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This article addresses some differences in psychopathology between men and women and asks the question, Why are women disadvantaged with respect to men when it comes to certain psychiatric disorders, such as mood disorders and Alzheimer's disease, and relatively advantaged when it comes to others, such as schizophrenia? Although there is much debate about the reasons for differing rates of psychiatric illness, it is generally agreed that most of the relative disadvantages that accrue to women do not take place until after puberty, boys being much more susceptible to psychological/psychiatric problems than girls (1). The marked sex differences in rates of illness that begin with the reproductive years suggest that the brain's hormonal environment during adulthood may be an important point of departure in the search for an explanation. That being said, it is recognized that the adult brain has earlier, during fetal life, been shaped or "organized" by its hormonal environment so that postpubertal effects act on an already sexually dimorphic organ (2, 3). It is also recognized that hormonally induced propensities are always expressed in a social context that powerfully shapes their expression.

Women and men are genetically very similar, except that different hormones enter the brain at different times and at different tempos, encouraging some brain cells to sprout more than others at time periods critical to brain development. Males and females are undifferentiated until the sixth week of gestation, when testes develop in males and begin to produce androgens. Follicle-stimulating hormone (FSH) is found in the pituitary glands of both sexes by fetal week 10, and its concentration increases dramatically, but only in females, between weeks 12 and 20 (4). FSH is thought to play a key role in fetal ovarian development, but the influence of ovarian secretions on the brain during fetal life is not nearly as well understood as that of testosterone (5). In humans, maximum CNS sensitivity to the organizational effects of gonadal steroids is presumed to occur between gestational weeks 14 and 16, when peak concentrations of testosterone are found in fetal serum (4). From then until puberty, the brain's hormonal environment is again very similar in females and males. Females reach sexual maturity earlier than males. Although the extent of this difference varies with genes, geography, and nutritional factors, it appears to be a fact in all mammals and, for good measure, in birds as well (6). During sexual maturity, hormone levels of women fluctuate cyclically over a much larger range than those of men. At female menopause, ovarian secretion shuts down. In men the testes continue to produce testosterone, which is partly converted to estradiol in the brain, but at an increasingly slower rate. In very old age, the

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brain hormonal environment is once again similar in the two sexes. These male/female contrasts are thought to play a part in the expression of many neuropsychiatric illnesses.

ALZHEIMER'S DISEASE

Women are disproportionally prone to Alzheimer's disease, even after adjustment for their longer survival (7–10). As many as 30%–50% of women older than 85 years suffer from a dementing process (7). Women's cognitive impairments may also be more severe than men's (11). Part of the increased understanding of the puzzle of Alzheimer's disease lies in the clarification of the effect of estrogens on neurotrophins, proteins that play both individual and combined roles in the sustenance of neural axons and dendrites and also in the growth of new nerve cells. This hormonal modulation of neurotrophins increases the connections among neuronal branches and maintains a complex system of communication in the brain (12). When estrogen levels drop at menopause, brain cells of women begin to degenerate at a faster pace than those of men. Men are relatively spared because their continuing testosterone secretion is converted, to some extent, to estradiol in the brain. This hypothesis has been supported by studies which show that estrogen replacement therapy prevents, or at least delays, the onset of Alzheimer's disease (13) and may even improve memory in Alzheimer's patients (14).

The neurotrophin route is only one of the ways in which estrogens may act to protect against Alzheimer's disease. Estrogens are also antioxidants, protecting neurons against β-amyloid, one of the proteins that accumulates in patients with Alzheimer's disease to produce neuronal degeneration (15, 16). Estrogens also modulate the secretion of acetylcholine in the hippocampus by their effect on choline acetyltransferase, an enzyme critical to the maintenance of memory functions (16, 17).

In summary, women's special vulnerability to Alzheimer's disease, a disease of neuronal degeneration, may be attributable—as is the case for osteoporosis and cardiovascular disease—to postmenopausal estrogen withdrawal.

SCHIZOPHRENIA

Men and women are more or less equally prone to develop schizophrenia, but the onset of symptoms is earlier in men (18). Possible explanations for this are 1) sexually dimorphic brain anatomy, 2) the disproportionately high incidence of birth injury in boys, 3) the differential effects of estrogens and androgens, 4) heavy exposure of male adolescents to alcohol and other toxic substances, and 5) the buffering action of earlier marriage among young women (19, 20). Schizophrenia in women is relatively mild in the first decade but increases in severity later, when the symptoms in men paradoxically taper off (21). This sex difference may, to some extent, be connected to the faster drop in dopamine and serotonin receptors with age in men (22). Women seem to respond better to antipsychotic drug treatment, at least when they are young (they need lower doses of antipsychotic drugs to get over an acute episode and to ward off future episodes) (23). The reason for this disparity is unknown. It has been attributed to better treatment compliance among women but also to the various antidopaminergic actions of estrogen hormones, such as the decrease in the rate of tyrosine hydroxylase gene transcription (24), tyrosine hydroxylase being the rate-limiting enzyme responsible for the synthesis of catecholamines (for a review of the several antidopaminergic actions of estrogens, see reference 25).

Not all clinical reports agree that estrogens play a protective role in schizophrenia (26). While the finding of later onset in schizophrenic women has been replicated numerous times (27), the onset age difference disappears when one studies familial schizophrenia (28–30). Do genetic influences in familial schizophrenia overshadow estrogen effects (31)? It is uncertain whether family liability in itself hastens onset age (32). Explanations other than the hormonal one exist for the sex discrepancy in age at onset, for instance, the impact of maternal obstetrical complications in bringing the age at onset forward preferentially in men. A recent study, however, suggests that maternal histories of obstetrical complications are equally prevalent among preschizophrenic men and women (33). Men have more negative symptoms than do women (34, 35) and, arguably, more brain abnormalities (36–38). These sex differences may be secondary to later environmental events but may also be primary, emerging from hormonal differences between male and female fetuses (39–42).

While late-onset schizophrenia is unquestionably more common in women, it has not been proven that this is related to estrogen withdrawal (43–45); nor has it been shown that the worsening of symptoms which sometimes occurs in schizophrenic women as they grow older correlates with decreasing estrogen levels (46). Nevertheless, Häfner's group (47–49) provides convincing epidemiologic and experimental evidence for the role of estrogens, particularly estradiol, in women's relative protection against psychosis. This protection is probably mediated through social factors. Estrogens have been conceptualized as protecting vulnerable neural circuits that come on-line during adolescence (50), thus delaying onset in prepsychotic females and permitting them to finish school, start a job, and establish interpersonal intimacy—all of these achievements subsequently conferring an advantage (51–53). Males, by contrast, frequently develop psychotic symptoms while still in school. Consequently, they have trouble completing their schooling, they never become proficient at a job, and they never develop the social skills required to get along in the world. This early start of illness may be responsible for the greater social deficits seen in men (54).

The protective effect for women, however, wanes in the fourth decade, at approximately the same time that women's estrogen levels begin to decline. Long-term studies (15 or more years after the beginning of illness) from around the world do not support outcome differences between men and women, although at 2 years, 5 years, and 10 years into the illness, most research shows women, as a group, doing significantly better than men (55–58). The "doing better" during the first decade of illness may be more related to premorbid competence, relative absence of substance abuse, and compliance with treatment than to hormones (although such behaviors may be hormone-dependent to some extent). The decline in female advantage in the second and third decades of illness, rather than being hormone-induced, may be caused by the greater impact on women than on men of the loss of family and other emotional supports (M.V. Seeman, manuscript submitted for publication).

The hypothesis about the protective effects of estrogens is bolstered by the observation that in pregnancy, when estrogen levels are steadily rising, women who have had recurrent acute episodes of schizophrenia do not usually break down (59, 60). However, they do suffer postpartum psychoses when estrogen levels have abruptly plummeted (61). In addition, psychotic symptoms are relatively exacerbated when estrogen levels are at their lowest during the menstrual cycle (62–64), and estrogen treatment has been shown to produce some beneficial effects in patients with schizophrenia (65).

Schizophrenia is thought to be a neurodevelopmental disorder with roots in critical phases of embryonic life, during which neurons fail to grow, to migrate to their appointed sites, or to make appropriate synaptic connections. As noted in the section on Alzheimer's disease, estrogens stimulate nerve growth factors and enhance neuronal survival. This occurs throughout the life cycle, from fetal development through puberty and into old age (42). The neural protection during the epoch of brain organization may be central to sex differences in schizophrenia (40).

In summary, in schizophrenia, the presence of estrogens at crucial time periods appears to confer an advantage that is lost upon estrogen withdrawal.

ALCOHOL DEPENDENCE

Like schizophrenia, alcohol dependence also starts earlier in men; but unlike schizophrenia, it remains three to five times more common in men than in women throughout the lifespan. In the United States, 24% of men, versus 5% of women, suffer an alcohol-related disorder during their lifetimes (66). While it has been reported that this ratio is rapidly changing, in conformity with social changes occurring in North America, it is also possible that social factors will never obliterate the sex difference. Androgens enhance the activity of alcohol dehydrogenase, the liver enzyme that is responsible for the elimination of alcohol (67). Efficient elimination protects against immediate subjective negative consequences and, thus, favors the early development of alcohol dependence in males. Alcohol dehydrogenase is less active in women, thereby discouraging heavy drinking but, by the same token, allowing greater absorption of the alcohol that is consumed and increasing the risk of alcohol toxicity.

Female alcohol users drink lesser quantities, which in the early years leads to fewer social, occupational, and legal problems. But the dependence process in women becomes "telescoped" (starts later than in men but reaches end stages sooner), so that long-term secondary effects of alcohol on internal organs are expressed at an earlier chronological age. In women, cognitive impairment secondary to alcohol-induced neuronal toxicity shows a pattern similar to that in men but occurs earlier in the course of a lifetime of drinking (68, 69).

Alcoholic women develop medical consequences and die as a result of them at a greater rate than alcoholic men. Women who drink shorten their lives by an average of 15 years, and their death rate is five times that of the general population of women; alcoholic men's death rate is three times that of other men (69).

In summary, while incidence and prevalence rates are greater among men, alcoholism leads to severe problems in the individual woman earlier than in the individual man.

ANXIETY DISORDERS

Women are more prone than men to essentially all anxiety disorders (70–73). Simple phobia is twice as common in women as in men. Phobic objects tend to be the same for men and women (animals, heights, blood, airplanes), but women score somewhat higher on fear questionnaires such as the Fear Survey Schedule (74), commonly used to assess the severity of phobias. The lifetime prevalence of social phobia is about 2% in the general population, and 70% of those affected are women (75). Uncomplicated panic disorder occurs in 20/1,000 women and about 8/1,000 men. Agoraphobia with or without panic attacks is found in nearly 8% of women versus 3% of men. The number of episodes increases premenstrually in affected women. The 1-year prevalence of generalized anxiety in the community at large is 1%–2% among men and 2%–5% among women (75).

A large study of a treated study group with posttraumatic stress disorder (PTSD) showed a rate of 11% in women and 7% in men (76). The investigators extrapolated from their data to estimate that 31% of women and 19% of men who are exposed to major trauma develop PTSD symptoms. In other words, when exposed to a traumatic life event, more women than men develop PTSD, and in addition, women make up 85% of the group whose symptoms last for over a year.

Because women complain of premenstrual and postpartum exacerbations of anxiety and panic states, hormonal fluctuations have been advanced as possible contributors to understanding the difference between the

sexes in anxiety disorders. All steroids modulate the γ-aminobutyric acid$_A$ ($GABA_A$)/benzodiazepine receptor, with progesterone metabolites acting as agonists and, therefore, as anxiolytics (77). In addition, estrogens have been shown to up-regulate the $GABA_A$/benzodiazepine receptor (78). It is possible that the cyclic withdrawal of progestins and estrogens "kindles" neuronal systems and promotes anxiety states by mechanisms similar to those which have been implicated in the provocation of perimenstrual epilepsy (79).

In summary, women suffer more than men from anxiety states, and there is some indication that women become more anxious during times of relatively low levels of circulating estrogen and progesterone. Ovarian steroids appear to act as anxiolytics. Their periodic physiologic withdrawal mimics anxiolytic withdrawal and could be responsible for women, as a group, being more sensitive than men to the anxiogenic effects of nonspecific stress.

MOOD DISORDERS

While the lifetime risk of bipolar or manic-depressive illness is approximately 1% for both sexes, unipolar depressions are twice as common in women as in men (80). Dysthymia is also twice as common in women. These differences between the sexes in prevalence are true, however, only for adults and do not emerge until adolescence (81). The meaning of puberty to adolescents is, of course, far more extensive and complex than could be surmised from studying only the direct effects of hormone levels on the brain. It has been suggested that the alterations in body shape that accompany puberty are, for cultural reasons, welcomed by young men but dreaded by young women, at least in industrialized countries (82). Males' and females' relationships with parents during the adolescent period also vary, with new-found independence perceived as positive in men and stressful in women (83). The literature on help seeking suggests that young women, once they are old enough to do so independently, seek treatment for psychological problems more frequently than young men (84). However, this fact alone could not explain the differential variance in community rates of both depression and anxiety. It is interesting that studies in developing countries such as India, Iraq, and New Guinea have not shown the doubling of rates of depression in women relative to those in men, but these surveys are confined to treated populations (85). A recent article from the National lnstitute of Mental Health Epidemiologic Catchment Area study (86), in which only the Los Angeles and New Haven data were used, reported that among Jews there was a 1:1 female/male ratio, which, the authors speculated, was due to low rates of alcoholism among Jewish males and, consequently, more depression among them. Social role, access to health care, and birth cohort effects have all been implicated in the determination of sex differences in depression in different population samples (87–89).

A few sex differences in course of illness in depression have also been noted. Women have more frequently recurring episodes. Women also report a greater number of individual symptoms. But when symptom severity is rated by the clinician rather than the patient, it is the same for both sexes (90).

Because of increasing awareness that both biological and sociocultural sex variables shape personality, investigators have searched for personality factors associated with sex role that are capable of explaining women's special vulnerability to depression (91, 92). It has been observed that women, to a greater degree than men, invest their emotions in interpersonal relationships. Consequently, they suffer from the impact of life events that take place not only in their own lives but also in the lives of their extended network of friends and relatives. However, this interesting hypothesis of why women might be more prone to depression, despite men and women experiencing equal numbers of personal life events, is not supported by the evidence, which suggests, to the contrary, that strong social networks (more prevalent among women than among men) protect against depression (93).

Another reported personality difference is that women internalize their feelings to a greater degree than do men and blame themselves for incompetence or failure, which leads to depression, while men blame others, which leads to anger. This is a classic view of depression that has been difficult to prove empirically. Still another difference between the sexes is a passive, ruminative style of coping with problems, which is more prevalent among women, and an active, distraction-oriented style, which is more common among men (94). Nolen-Hoeksema has argued that this personality difference accounts for at least some of the sex variation in depression (94). Conflicting and changing social expectations of women and the higher rates of sexual abuse of girls during childhood and adolescence have also been considered as possible explanations for high rates of depression, and also of anxiety disorders, in women (75, 90). Psychological and social variables that distinguish women and men almost certainly apply to psychiatric disorders other than mood disorders, but they have been most intensely studied in the context of depression.

In summary, many factors seem to play a greater direct role in mood disorders than do female hormones. Personality and responses to stress are, however, influenced to some degree by hormones.

DISCUSSION

It appears that female hormones—estrogens in particular—exert potent effects on the expression of various forms of psychopathology. The literature on schizophrenia suggests that estrogens preserve the integrity of neuronal circuits. The literature on Alzheimer's disease suggests that estrogen withdrawal renders women especially vulnerable to that disorder. In

alcoholism, the absence of male hormones interferes with liver enzyme elimination of alcohol and, consequently, increases the risk of toxicity in women. The literature on depression and anxiety holds female hormones indirectly responsible for the greater prevalence of these disorders in women. It is not that estrogens directly dampen mood, although progestins may (95), but that the off-and-on binding to intranuclear estrogen receptors in the brain somehow renders women vulnerable to stress, perhaps through glucocorticoid-induced neuronal toxicity.

Estrogens—notably estradiol—play an active organizing role in the developing brain and a crucial maintenance role in the aging brain. Among other functions, they protect neurons against both developmental dysfunction (i.e., schizophrenia) and degenerative dysfunction (i.e., Alzheimer's disease). This action, as well as the antioxidant, antidopaminergic, and cholinergic actions of estradiol, can explain most of the sex differences seen in these two diseases. Parallel to their protective role against neuronal degeneration and/or impairment of neuronal development, it is likely that estrogens are also protective against the toxic effects of alcohol on nerve cells. But the higher blood levels of alcohol and the early menopause brought about by heavy alcohol use may account for women's cognitive decline after relatively short drinking histories. Men are supplied with estradiol into their old age, because estradiol continues to be synthesized intraneuronally from testosterone through the conversion enzyme neural aromatase.

The cyclic nature of estrogen secretion from puberty to menopause and, subsequently, its almost total withdrawal may account for the special vulnerability of women to mood and anxiety disorders. Recurrent estrogen withdrawal, starting in the early teens, may interfere with one of the natural functions of estrogen, the ability to neutralize the effects of glucocorticoids released during stress (96). This explanation is speculative but fits the epidemiologic evidence that the high prevalence of these conditions in women is evident only after puberty.

Hormone receptors are present from early fetal life in the hypothalamus, organizing brain circuitry, setting the stage for puberty, regulating subsequent adult sexual behavior, and controlling the interaction of the hypothalamic-pituitary-adrenal-gonadal axis from puberty onward. Most relevant to psychiatric disease, gonadal hormone receptors are seen in regions of the brain that mediate both cognition and affect. During development and also during adult life (with variations from one time period to another), gonadal steroid receptors are expressed in the nuclei of the septum and the diagonal band of Broca, the hippocampus, the allocortex, the isocortex, and the amygdaloid complex (97). The best-studied receptor is the one for estradiol, known to regulate neuronal function in a number of important ways. Gonadal hormone receptors act as genetic transcription factors. The attachment of estradiol to its receptor is accompanied by a receptor phosphorylation that leads to a conformational change in the receptor and the subsequent binding of the estradiol receptor complex to many DNA sequences at a variety of chromosomal sites, all of which respond to the hormone stimulus (98). In addition, more is now known about indirect (nongenomic) effects of estrogens on nerve cells in the brain. For example, by acting directly on membrane receptors, estrogens decrease behaviors mediated by the dopamine D_2 receptor (25).

Various neurotrophins, known to be neuroprotective, up-regulate the density of nuclear estrogen binding sites, while at the same time, estradiol up-regulates the level of the neurotrophins, synergizing their neuroprotective role (97). That role is to prevent cell death, to promote growth of cells and parts of cells, and to enhance neural communication. There is evidence that women are more sensitive to perceived stress than men—for instance, that more women than men develop posttraumatic stress syndromes after being exposed to a stressor (76). While the interaction among glucocorticoids, neurotrophins, and estrogens is complex and as yet unclear (99), it is possible that estrogen cyclicity may render women inherently more vulnerable to the neurotoxic processes engendered by stress hormones. Indeed, recent life stresses were found to be the most important determinants of depression in the 1993 study of depression in female twins by Kendler et al. (100).

In summary, there are many reasons to believe that evolutionary imperatives have assigned a special neuroprotective but also a stress-sensitive mediating role to female hormones (specifically to their cyclicity), which consequently confers both psychiatric advantage and disadvantage to women. During the childbearing years, women are comparatively shielded from the more severe psychotic illnesses but are more vulnerable than men to depression and anxiety.

REFERENCES

1. Earls F: Sex differences in psychiatric disorders: origins and developmental influences. Psychiatr Developments 1987; 1:1–23
2. Pilgrim C, Reisert I: Differences between male and female brains—developmental mechanisms and implications. Horm Metab Res 1992; 24:353–359
3. Breedlove SM: Sexual differentiation of the human nervous system, in Annual Review of Psychology. Edited by Porter LW, Rosenzweig MR. Palo Alto, Calif, Annual Reviews, 1994, pp 389–418
4. Finegan J, Bartleman B, Wong PY: A window for the study of prenatal sex hormone influences on postnatal development. J Genet Psychol 1988; 150:101–112
5. Rubinow DR, Schmidt PJ: Androgens, brain, and behavior. Am J Psychiatry 1996; 153:974–984
6. Caswell H, Weeks DE: Two-sex models: chaos, extinction, and other dynamic consequences of sex. American Naturalist 1986; 128:707–735
7. Bachman DL, Wolf PA, Linn R, Knoefel JE, Cobb J, Belanger A, D'Agostino RB, White LR: Prevalence of dementia and probable senile dementia of the Alzheimer type in the Framingham Study. Neurology 1992; 42:115–119
8. Bachman DL, Wolf PA, Linn RT, Knoefel JE, Cobb JL, Belanger AJ, White LR, D'Agostino RB: Incidence of dementia and probable Alzheimer's disease in a general population: the Framingham Study. Neurology 1993; 43:515–519

9. Canadian Study of Health and Aging Working Group: Canadian study of health and aging: study methods and prevalence of dementia. Can Med Assoc J 1994; 150:899–913
10. Tang MX, Jacobs D, Stern Y, Marder K, Schofield P, Gurland B, Andrews H, Mayeux R: Effect of oestrogen during menopause on risk and age at onset of Alzheimer's disease. Lancet 1996; 348:429–432
11. Henderson VW, Buckwalter JG: Cognitive deficits of men and women with Alzheimer's disease. Neurology 1994; 44:90–96
12. McEwen BS: Non-genomic and genomic effects of steroids on neural activity. Trends Pharmacol Sci 1991; 12:141–147
13. Paganini-Hill A, Henderson VW: Estrogen replacement therapy and risk of Alzheimer's disease. Arch Intern Med 1996; 156: 2213–2217
14. Henderson VW, Paganini-Hill A, Emanuel CK, Dunn ME, Buckwalter JG: Estrogen replacement therapy in older women. Arch Neurol 1994; 51:896–900
15. Goodman Y, Bruce AJ, Cheng B, Mattson MP: Estrogens attenuate and corticosterone exacerbates excitotoxicity, oxidative injury and amyloid B-peptide toxicity of hippocampal neurons. J Neurochem 1996; 66:1836–1844
16. Wickelgren I: Estrogen stakes claim to cognition. Science 1997; 276:675–678
17. McEwen BS: Steroid hormones are multifunctional messengers to the brain. Trends in Endocrinology and Metabolism 1991; 2:62–67
18. Häfner H, an der Heiden W: Epidemiology of schizophrenia. Can J Psychiatry 1997; 42:139–151
19. Lewine RJR, Seeman MV: Gender, brain, and schizophrenia: anatomy of differences/differences of anatomy, in Gender and Psychopathology. Edited by Seeman MV. Washington, DC, American Psychiatric Press, 1995, pp 131–158
20. Jablensky A, Cole SW: Is the earlier age at onset of schizophrenia in males a confounded finding? Br J Psychiatry 1997; 170:234–240
21. Ciompi L: The influence of aging on schizophrenia. Triangle 1993; 32:25–31
22. Wong DF, Wagner HN Jr, Dannals RF, Links JM, Frost JJ, Ravert HT, Wilson AA, Rosenbaum AE, Gjedde A, Douglass KH, Petronis JD, Folstein MF, Toung JKT, Burns HD, Kuhar MJ: Effects of age on dopamine and serotonin receptors measured by positron tomography in the living human brain. Science 1984; 226:1393–1396
23. Seeman MV: Sex differences in predicting neuroleptic response, in The Prediction of Neuroleptic Response. Edited by Gaebel W, Awad AG. Vienna, Springer-Verlag, 1995, pp 51–64
24. Blum M, McEwen BS, Roberts JL: Transcriptional analysis of tyrosine hydroxylase gene expression in the tuberoinfundibular dopaminergic neurons of the rat arcuate nucleus after estrogen treatment. J Biol Chem 1987; 262:817–821
25. DiPaolo T: Modulation of brain dopamine transmission by sex steroids. Rev Neurosci 1994; 5:27–42
26. Castle DJ, Abel K, Takei N, Murray RM: Gender differences in schizophrenia: hormonal effect or subtypes? Schizophr Bull 1995; 21:1–12
27. Faraone SV, Chen WJ, Goldstein JM, Tsuang MT: Gender differences in age at onset of schizophrenia. Br J Psychiatry 1994; 164:625–629
28. Albus M, Maier W: Lack of gender differences in age at onset in familial schizophrenia. Schizophr Res 1995; 18:51–57
29. DeLisi LE: Age of onset in familial schizophrenia. Arch Gen Psychiatry 1994; 51:334–335
30. Gorwood P, Leboyer M, Jay M, Payan C, Feingold J: Gender and age at onset in schizophrenia: impact of family history. Am J Psychiatry 1995; 152:208–212
31. Alda M, Ahrens B, Lit W, Dvorakova M, Labelle A, Zvolsky P, Jones B: Age of onset in familial and sporadic schizophrenia. Acta Psychiatr Scand 1996; 93:447–450
32. Kendler KS, Karkowski-Shuman L, Walsh D: Age at onset in schizophrenia and risk of illness in relatives: results from the Roscommon family study. Br J Psychiatry 1996; 169:213–218
33. Hultman CM, Ohman A, Cnattingius S, Wieselgren IM, Lindstrom LH: Prenatal and neonatal risk factors for schizophrenia. Br J Psychiatry 1997; 170:128–133
34. Shtasel DL, Gur RE, Gallacher F, Heimberg C, Gur RC: Gender differences in the clinical expression of schizophrenia. Schizophr Res 1992; 7:225–231
35. Gur RE, Petty RG, Turetsky BI, Gur RC: Schizophrenia throughout life: sex differences in severity and profile of symptoms. Schizophr Res 1996; 21:1–12
36. Cowell PE, Kostianovsky DJ, Gur RC, Turesky BI, Gur RE: Sex differences in neuroanatomical and clinical correlations in schizophrenia. Am J Psychiatry 1996; 153:799–805
37. Reite M, Sheeder J, Teale P, Adams M, Richardson D, Simon J, Jones RH, Rojas DC: Magnetic source imaging evidence of sex differences in cerebral lateralization in schizophrenia. Arch Gen Psychiatry 1997; 54:433–440
38. Schlaepfer TE, Harris GJ, Tien AY, Peng LW, Lee S, Federman EB, Chase GA, Barta PE, Pearlson GD: Decreased regional cortical gray matter volume in schizophrenia. Am J Psychiatry 1994; 151:842–848
39. Lewis DW, Diamond MC: The influence of gonadal steroids on the asymmetry of the cerebral cortex, in Brain Asymmetry. Edited by Davidson RJ, Hugdahl K. Cambridge, Mass, MIT Press, 1995, pp 31–50
40. Seeman MV, Lang M: The role of estrogens in schizophrenia gender differences. Schizophr Bull 1990; 16:185–194
41. Seeman MV: The role of estrogen in schizophrenia. J Psychiatry Neurosci 1996; 21:123–127
42. Toran-Allerand CD: The estrogen/neurotrophin connection during neural development: is co-localization of estrogen receptors with the neurotrophins and their receptors biologically relevant? Dev Neurosci 1996; 18:36–41
43. Castle DJ, Murray RM: The epidemiology of late-onset schizophrenia. Schizophr Bull 1993; 19:691–700
44. Howard R, Almeida O, Levy R: Phenomenology, demography and diagnosis in late paraphrenia. Psychol Med 1994; 24:397–410
45. Pearlson G, Rabins P: The late-onset psychoses: possible risk factors. Psychiatr Clin North Am 1988; 11:15–32
46. Salokangas RKR: Gender and the use of neuroleptics in schizophrenia: further testing of the oestrogen hypothesis. Schizophr Res 1995; 16:7–16
47. Häfner H, Behrens S, De Vry J, Gattaz WF: An animal model for the effects of estradiol on dopamine-mediated behavior: implications for sex differences in schizophrenia. Psychiatry Res 1991; 38:125–134
48. Häfner H, Behrens S, De Vry J, Gattaz WF: Oestradiol enhances the vulnerability threshold for schizophrenia in women by an early effect on dopaminergic transmission. Eur Arch Psychiatry Clin Neurosci 1991; 241:65–68
49. Riecher-Rössler A, Häfner H: Schizophrenia and oestrogens—is there an association? Eur Arch Psychiatry Clin Neurosci 1993; 242:323–328
50. Lewis DA: Development of the prefrontal cortex during adolescence: insights into vulnerable neural circuits in schizophrenia. Neuropsychopharmacology 1997; 16:385–398
51. Lewine RRJ: Gender and schizophrenia, in Handbook of Schizophrenia, vol 3. Edited by Tsuang M, Simpson J. Amsterdam, Elsevier, 1988, pp 131–158
52. Foerster A, Lewis S, Owen M, Murray R: Pre-morbid adjustment and personality in psychosis: effects of sex and diagnosis. Br J Psychiatry 1991; 158:171–176
53. Mueser KT, Bellack AS, Morrison RL, Wixted JT: Social competence in schizophrenia: premorbid adjustment, social skill, and domains of functioning. J Psychiatr Res 1990; 24:51–63
54. Häfner H, Nowotny B, Loffler W, an der Heiden W, Maurer K: When and how does schizophrenia produce social deficits? Eur Arch Psychiatry Clin Neurosci 1995; 246:17–28
55. Harrison G, Croudace P, Mason C, Glazebrook C, Medley I: Predicting the long-term outcome of schizophrenia. Psychol Med 1996; 26:697–705
56. Jonsson H, Nyman AK: Predicting long-term outcome in schizophrenia. Acta Psychiatr Scand 1991; 83:342–346
57. Opjordsmoen S: Long-term clinical outcome of schizophrenia with special reference to gender differences. Acta Psychiatr Scand 1991; 83:307–313

58. Salokangas RKR, Stengard E: Gender and short-term outcome in schizophrenia. Schizophr Res 1990; 3:333–345
59. Chang SS, Renshaw DC: Psychosis and pregnancy. Compr Ther 1986; 12:36–41
60. Krener P, Simmons MK, Hansen RL, Treat JN: Effect of pregnancy on psychosis: life circumstances and psychiatric symptoms. Int J Psychiatry Med 1989; 19:65–84
61. Kendell RE, Chalmers JC, Platz C: Epidemiology and puerperal psychoses. Br J Psychiatry 1987; 150:662–673
62. Gattaz WF, Vogel P, Riecher-Rössler A, Soddu G: Influence of the menstrual cycle phase on the therapeutic response in schizophrenia. Biol Psychiatry 1994; 36:137–139
63. Hallonquist J, Seeman MV, Lang M, Rector N: Variation in symptom severity over the menstrual cycle of schizophrenics. Biol Psychiatry 1993; 33:207–209
64. Riecher-Rössler A, Häfner H, Stumbaum M, Maurer K, Schmidt R: Can estradiol modulate schizophrenic symptomatology? Schizophr Bull 1994; 20:203–214
65. Kulkarni J, de Castella A, Smith D, Taffe J, Keks N, Copolov D: A clinical trial of the effects of estrogen in acutely psychotic women. Schizophr Res 1996; 20:247–252
66. Lex B: Gender differences and substance abuse. Advances in Substance Abuse 1991; 4:225–296
67. Lakota GN, Barkov NK: The role of testosterone in the development of experimental alcoholism. Bull Narc 1980; 32:41–48
68. Lex BW: Alcohol and other psychoactive substance dependence in men and women, in Gender and Psychopathology. Edited by Seeman MV. Washington, DC, American Psychiatric Press, 1995, pp 311–358
69. Greenfield SF: Women and substance use disorders, in Psychopharmacology and Women. Edited by Jensvold MF, Halbreich U, Hamilton JA. Washington, DC, American Psychiatric Press, 1996, pp 299–321
70. Bland RC, Newman SC, Orn H: Epidemiology of psychiatric disorders in Edmonton. Acta Psychiatr Scand Suppl 1988; 338:1–80
71. Kessler RC, McGonagle KA, Zhao S, Nelson CB, Hughes M, Eshleman S, Wittchen H, Kendler KS: Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States: results from the National Comorbidity Survey. Arch Gen Psychiatry 1994; 51:8–19
72. Offord DR, Boyle MH, Campbell D, Goering P, Lin E, Wong M, Racine Y: One-year prevalence of psychiatric disorder in Ontarians 15 to 64 years of age. Can J Psychiatry 1996; 41:559–563
73. Robins LN, Regier DA (eds): Psychiatric Disorders in America: The Epidemiologic Catchment Area Study. New York, Free Press, 1991
74. Wolpe J, Lang P: A fear survey schedule for use in behavior therapy. Behav Res Ther 1964; 2:27–30
75. Yonkers KA, Gurguis G: Gender differences in the prevalence and expression of anxiety disorders, in Gender and Psychopathology. Edited by Seeman MV. Washington, DC, American Psychiatric Press, 1995, pp 113–130
76. Yonkers KA, Ellison JM: Anxiety disorders in women and their pharmacological treatment, in Psychopharmacology and Women. Edited by Jensvold MF, Halbreich U, Hamilton JA. Washington, DC, American Psychiatric Press, 1996, pp 261–285
77. Majewska MD: Neurosteroids: endogenous modulators of the GABA-A receptor; mechanism of action and physiological significance. Prog Neurobiol 1992; 38:379–395
78. Maggi A, Perez J: Estrogen-induced up-regulation of gamma-amino butyric receptors in the CNS of rodents. J Neurochem 1986; 47:1793–1797
79. Narbone MC, Ruello C, Oliva A, Baviera G, D'Amico D, Bramanti P, Di Perri R: Hormonal dysregulation and catamenial epilepsy. Funct Neurol 1990; 5:49–53
80. Kessler RC, McGonagle KA, Swartz M, Blazer DG, Nelson CB: Sex and depression in the National Comorbidity Survey, I: lifetime prevalence, chronicity and recurrence. J Affect Disord 1993; 29:85–96
81. Buchanan CM, Becker JB, Eccles JS: Are adolescents the victims of raging hormones? evidence for activational effects of hormones on moods and behavior at adolescence. Psychol Bull 1992; 111:62–107
82. Woodside DB, Kennedy SH: Gender differences in eating disorders, in Gender and Psychopathology. Edited by Seeman MV. Washington, DC, American Psychiatric Press, 1995, pp 253–268
83. McDermott JF Jr, Robillard AB, Char WF, Hsu J, Tseng WS, Ashton GC: Reexamining the concept of adolescence: differences between adolescent boys and girls in the context of their families. Am J Psychiatry 1983; 140:1318–1322
84. Almqvist F: Sex differences in adolescent psychopathology. Acta Psychiatr Scand 1986; 73:295–306
85. Shaw J, Kennedy SH, Joffe RT: Gender differences in mood disorders: a clinical focus, in Gender and Psychopathology. Edited by Seeman MV. Washington, DC, American Psychiatric Press, 1995, pp 89–111
86. Levav I, Kohn R, Golding JM, Weissman MM: Vulnerability of Jews to affective disorders. Am J Psychiatry 1997; 154:941–947
87. Harris T, Surtees P, Bancroft J: Is sex necessarily a risk factor for depression? Br J Psychiatry 1991; 158:708–712
88. Paykel ES: Depression in women. Br J Psychiatry 1991; 158 (suppl 10):22–29
89. Silverstein B, Perlick D: Gender differences in depression: historical changes. Acta Psychiatr Scand 1991; 84:327–331
90. Hamilton JA, Grant M, Jensvold MF: Sex and treatment of depressions: when does it matter? in Psychopharmacology and Women. Edited by Jensvold MF, Halbreich U, Hamilton JA. Washington, DC, American Psychiatric Press, 1996, pp 241–257
91. Brown LS, Ballou M: Personality and Psychopathology: Feminist Reappraisals. New York, Guilford Press, 1992
92. Boyce P, Parker G, Barnett B, Cooney M, Smith F: Personality as a vulnerability factor to depression. Br J Psychiatry 1991; 159:106–114
93. Cohen S, Wills TA: Stress, social support, and the buffering hypothesis. Psychol Bull 1985; 98:310–357
94. Nolen-Hoeksema S: Sex Differences in Depression. Stanford, Calif, Stanford University Press, 1990
95. Schumaker M, Baulieu EE: Neurosteroids: synthesis and function in the central and peripheral nervous systems. Ciba Found Symp 1995; 191:90–106
96. Mizoguchi K, Tatshuhide T, De-Hua C, Tabira T: Stress induces neuronal death in the hippocampus of castrated rats. Neurosci Lett 1991; 138:157–160
97. Miranda RC, Sohrabji F: Gonadal steroid receptors: possible roles in the etiology and therapy of cognitive and neurological disorders. Annual Reports in Medicinal Chemistry 1996; 31: 11–20
98. Sohrabji F, Miranda RC, Toran-Allerand CD: Estrogen differentially regulates estrogen and nerve growth factor receptor mRNAs in adult sensory neurons. J Neurosci 1994; 14:459–471
99. Sapolsky RM: Stress, glucocorticoids, and damage to the nervous system: the current state of confusion. Stress 1996; 1:1–19
100. Kendler KS, Kessler RC, Neale MC, Heath AC, Eaves LJ: The prediction of major depression in women: toward an integrated etiologic model. Am J Psychiatry 1993; 150:1139–1148