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Sex steroids and schizophrenia

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Abstract The peak in incidence for schizophrenia is during late adolescence for both sexes, but within this time frame the peak is both earlier and steeper for males. Additionally, women have a second peak in incidence following menopause. Two meta-analyses have reported that men have an overall ~40% greater chance of developing schizophrenia than do women (Aleman et al., 2003; McGrath et al., 2004). These and other findings have led to the suggestion that ovarian hormones may be protective against schizophrenia. Less explored is the potential role of testosterone in schizophrenia, although disruptions in steroid levels have also been reported in men with the illness. The relationship between increased gonadal hormone release *per se* and peri-adolescent vulnerability for psychiatric illness is difficult to tease apart from other potentially contributory factors in clinical studies, as adolescence is a turbulent period characterized by many social and biological changes. Despite the obvious opportunity provided by animal research, surprisingly little basic science effort has been devoted to this important issue. On the other hand, the animal work offers an understanding of the many ways in which gonadal steroids exert a powerful impact on the brain, both shaping its development and modifying its function during adulthood. Recently, investigators using preclinical models have described a greater male vulnerability to neurodevelopmental insults that are associated with schizophrenia; such studies may provide clinically relevant insights into the role of gonadal steroids in psychiatric illness.

Keywords Estrogen · Testosterone · Psychosis · Gonadal hormones · Sex differences · Animal models

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Schizophrenia is most often associated with its positive symptoms, such as hallucinations, delusions, and disorganized thought processes, which can be effectively treated with antipsychotic drugs. The affinity of so-called "neuroleptics" for the dopamine 2 (D_2) receptor correlates with therapeutic efficacy for these symptoms [1]. On the other hand the negative symptoms, including poor social functioning and apathy (experienced by roughly one third of patients), and the cognitive symptoms, including disrupted executive functioning, reduced attentional capacity, and memory impairments (experienced by nearly all patients), appear relatively impervious to antipsychotic medication [2]. Despite decades of research, the etiology of this serious neuropsychiatric illness, which affects nearly 1% of the world's population [3], remains unknown. A clear genetic component to the disorder exists; however, gene by environment factors are also known to play a role. For instance, the concordance rate for schizophrenia among monozygotic twins, while much higher than for non-twin siblings, is still only 50% [4]. Recent work estimates that as much as 80% of the genetic liability for schizophrenia is accounted for by gene by environment interactions [5]. One attractive hypothesis is that schizophrenia is a neurodevelopmental disorder, in which the events that trigger neuropathology in genetically vulnerable individuals occur much earlier in life than onset of the symptoms required for

clinical diagnosis. In this conceptualization, an early insult to the brain could remain undetected until normal maturational developmental processes bring the structures affected by the insult 'on-line' [6]. This would explain how pre- and perinatal events confer risk for schizophrenia, which does not clinically manifest until adolescence.

1 Sex differences in schizophrenia

Kraepelin was the first to report that first-time hospitalization for schizophrenia occurs earlier for men compared to women [7], an observation that has been replicated dozens of times [8]. The finding was originally misattributed to a sex difference in the latency between illness onset and first admission. It was thought that women tolerated the illness better than men, perhaps because of gender-specific social roles or the presence of milder symptoms in women. This explanation appeared less likely after a case register study of both Danish and German populations found that the sex difference in age of first admission is present in both employed and unemployed patients, and that the severity of symptoms at first admission is equivalent between men and women [9]. This study was part of the ABC (Age, Beginning, Course) Schizophrenia Study, a large-scale, primarily epidemiological project undertaken to determine the factors contributing to the sex difference in age of first admission. Subsequent reports in this series conclusively demonstrated that this finding is due to a true sex difference in age of onset, and not to artifacts such as cultural factors or sex differences in diagnostic procedures, help-seeking behavior, or occupational status [10–15]. Incidence rates in males reach a steep peak around 15–24 years, whereas females don't reach their first peak until between age 20–29 years; the mean age of onset is 3–4 years earlier in men compared to women [10, 16]. The one exception to this rule appears to be among cases of familial schizophrenia, in which women show the same, earlier age of onset as males [17, 18]. The presence of a sex difference in age of onset for sporadic but not familial cases of schizophrenia suggests that estrogen may buffer females against an environmental insult that increases risk for schizophrenia. This possibility may be more easily addressed using preclinical models of psychiatric illness (*see below*). The notion that estrogen raises the vulnerability threshold for developing schizophrenia is supported by the finding that earlier puberty in females is associated with a delayed onset of the illness [19]. Interestingly, the opposite relationship is observed in men—earlier puberty appears to predict earlier illness onset—although the association did not reach significance in this study [19]. Further suggestive of a protective role for estrogen is the fact that a second, more modest peak in incidence occurs for women (but not men) between the ages of 45–54 years—i.e., following menopause [10, 14, 16].

The question of whether a sex difference exists in lifetime incidence of schizophrenia was historically controversial. Studies reporting greater lifetime incidence of schizophrenia among men were initially disregarded as being attributable to other confounding factors [10, 14]—for instance, age range (women are more likely to develop schizophrenia late in life than are men), hospital bias (men may be more likely to be hospitalized) and/or diagnostic criteria (narrow criteria for schizophrenia may exclude more women than men). Since then, the problem of age range has been resolved by including older patients in the sample population, and careful studies have actually failed to find evidence for a sex bias in either hospital admission or diagnosis [20, 21]. Finally, two systematic meta-analyses conducted in the last decade have both concluded that men have an overall ~40% greater chance of developing schizophrenia than do women, even when such factors are taken into account [22, 23]. This has important implications for the etiology of the illness—rather than simply mitigating symptoms and delaying relapses, estrogen exposure in females may in fact reduce lifetime risk, through mechanisms that may be distinct from its neuroleptic-like actions on symptom expression. Animal models of psychiatric illness may be particularly well suited to address this possibility.

Although women clearly have an elevated vulnerability threshold for developing schizophrenia, once the illness sets in it was thought that both the symptom severity and course of the illness were equivalent between the sexes [9, 24]. Part of the evidence in support of this view came from the ABC study, which reported a parallel progression of early illness milestones [25]. In contrast, several other groups have reported that men show poorer premorbid adjustment and more rapid functional deterioration as illness onset approaches, as compared to women [26, 27]. On the basis of these findings as well as those generated from studies of chronically ill patient populations, another view of illness course has emerged—namely, that women experience a less severe course of the illness over the long-term, characterized by shorter hospital stays, fewer relapses, better response to medication, and superior functioning and social adjustment [28–34].

The investigation of sex differences in illness course is complicated by several factors. The first is that there is no practical way to study the long-term course of schizophrenia in unmedicated patients, and women clearly have a greater response to neuroleptic drug treatment. Measures that are highly correlated with the therapeutic response to neuroleptic drugs (i.e., reductions in plasma levels of the dopamine metabolite homovanillic acid and increases in plasma levels of prolactin) are greater in women compared

to men [35, 36]. Similarly, the identical treatment dose results in higher plasma neuroleptic levels in women compared to men [35]. In practice, this means that the dose necessary to achieve therapeutic efficacy is lower in women—in some cases, by as much as half [37]. However, the fact that women show a greater degree of symptom improvement in response to medication does not by itself indicate that they suffer from a less severe form of the illness. Actually, the reason that some drugs require a higher dose in males may have more to do with the activity of liver enzymes involved in drug metabolism. For instance, olanzapine, clozapine, and haloperidol are metabolized by liver cytochrome P450 isoenzyme CYP1A2, which is more active in men than women [38]; this probably explains why plasma concentrations of olanzapine in women are reportedly twice that in men after dose, body mass index, age, and smoking status (which can all also impact metabolism of neuroleptics) are controlled [39]. In contrast, risperidone is metabolized by two liver enzymes, one of which is less active in women (CYP2D6) and the other of which is more active in women (CYP3A4)—perhaps consequently, plasma concentrations are equivalent between the sexes following identical doses [40]. Drug metabolism in women is regulated by estrogen, fluctuating across the menstrual cycle and changing as a consequence of oral contraceptive use, pregnancy, and menopause (reviewed by [40]). The greater degree of symptom improvement in women over the course of the illness is therefore somewhat unsurprising given the greater pharmacological responsivity of females (which also results in their experiencing adverse side effects more often than men). Because questions about illness *course* (as opposed to *onset*) must be answered in chronically medicated patients, it remains unknown whether men and women might experience differences in the natural, unmitigated course of the illness.

Another factor that could contribute to a more advantageous course of illness among women is their later age of onset. In general, earlier age of onset for schizophrenia is correlated with greater illness severity and poorer prognosis [41]. By the time the illness sets in for women, they are typically already settled into important family and professional roles that provide some stability, as well as a support network. Indeed, when first signs of mental illness appear, significantly more women than men are employed, are living independently, and are married or in stable partnerships (the difference in this last is especially pronounced given that men tend to marry later than women) [13], and these differences persist over time [42]. The social disadvantage conferred by an earlier age of illness onset could therefore account for the poorer long-term outcome that is commonly reported for men compared to women. On the other hand the recent findings from a prospective longitudinal study, which has studied an outpatient psychiatric population for the last two decades, do not support the notion that sex differences in social advantage at age of onset explain sex differences in outcome [32, 43]. Compared to men, women who had a similar age of onset (i.e., earlier than is typical for females) in this sample still had a lower percentage of psychotic activity over the course of the illness, and they also experienced a significant improvement in psychotic activity over the 20 year period, which was not the case for men. Measures of both global functioning and recovery were found to be superior in women as well. Interestingly, the female advantage in outcome was found for other psychotic disorders in addition to schizophrenia, whereas no sex difference in outcome was found for nonpsychotic psychiatric illnesses [32, 43]. This suggests that the most profound impact of estrogen is in mitigating psychotic symptoms associated with psychiatric illness, regardless of the illness diagnosis.

There is additional evidence that a person's sex biases which illness symptoms he or she is most likely to express. Numerous studies have shown that both the number and severity of negative symptoms, including "deficit states", is greater in men than women with schizophrenia [33, 34, 44, 45]. For instance, among first episode patients, men more commonly exhibit behaviors such as self-neglect, social withdrawal, and lack of interest in securing employment [25]. The greater male tendency towards negative symptoms and poorer functioning has been found even among a population of "ultra high risk" individuals; i.e., those showing prodromal symptoms but who have not yet converted to psychosis [46]. The greater male tendency towards negative symptoms is significant because, unlike positive symptoms, their severity is highly correlated with both social disability and reduced social status [25]. Additionally, the greater prevalence of alcohol and substance abuse in men compared to women with schizophrenia [19, 25] could contribute to the poorer long-term prognosis of men will the illness. On the other hand, women are more likely to present with affective symptoms (mood disturbances including depression), and to have the severity of their positive symptoms covary with the severity of their affective symptoms [45, 47].

Another way to approach the question of potential sex differences in illness severity is to examine alterations in neuropsychological performance, functional neuroimaging, and/or brain morphology among men and women with schizophrenia. Unfortunately it is terribly difficult to reach many generalizable conclusions from this literature, perhaps due to the many methodological differences between studies and, at least in the case of neuroimaging studies, often relatively small sample sizes. That being said, the trend most frequently observed is one that favors

females in terms of cognitive functioning and structural integrity of the brain. Most commonly, men with schizophrenia show greater ventricular enlargement and cortical atrophy relative to healthy men than do schizophrenic women relative to healthy women [48–52], Almost as often, no sex differences are found in these measures [42, 53, 54]. Much more infrequently a male advantage is reported, but such studies do exist [55, 56]. It is important to remember that, similar to other indices of illness course, measures of brain structure and function are not immune to the complexities inherent in characterizing a population of chronically medicated individuals. As discussed above, men require significantly higher doses of neuroleptics than women in order to achieve therapeutic efficacy, and therapeutic dose is defined as the lowest that provides relief from (primarily) psychosis, not one that restores cognitive deficits or mitigates the effects of long-term illness on brain morphology and function. Concerns over this issue can be overcome if it can be demonstrated that, within a sex, duration of neuroleptic treatment is not correlated with changes in the measure of interest.

Another significant challenge to the investigation of sex differences in schizophrenia is the fact that the male/female ratio for admission to inpatient services is consistently high. Therefore, even if the actual sex ratio for schizophrenia were equal, the access to potential subjects is not. This is why most studies have a high male to female ratio. Although this ratio can be kept similar between schizophrenic and control study populations, this can potentially lead to a bias for finding effects in males only, simply because comparisons between female patient and control groups are underpowered. One approach to this problem is to include equal numbers of men and women in the study sample. At first blush this may appear to be the optimal solution, but it may not be in all cases, especially when the sample population is inpatient. Because the inpatient population is both a) more ill than the outpatient one and b) predominantly male, female inpatients may suffer from a more severe form of the illness compared to the average woman with schizophrenia. Thus the danger with this approach is that it could introduce an artificial bias towards underestimating or entirely masking sex differences in the dependent variable(s) of interest. Indeed, studies that find no sex effect or the rare cases where female patients are found to be more affected are usually conducted on inpatient populations, especially institutions. In contrast, those that have found males to be more affected are usually conducted on outpatient populations. (For a discussion of how sampling biases may impact studies of sex differences in schizophrenia, see [57, 58]). Finally, because of the sex difference in age of onset, studies that control for age will describe a male patient population that has been ill for longer and has a longer history of neuroleptic treatment. Whether schizophrenia is a progressive illness and what may be the long-term neural consequences of neuroleptic drug treatment are two of the longest-standing controversies in the clinical literature, but until these important issues are resolved, arguably the best approach is to study patients at first episode. Of course, the first episode population presents a special problem for those interested in sex differences—controlling for age will select for either a female population that has an atypically early age of onset or for a male population with an atypically late age of onset. Additionally, questions about long-term illness course cannot be answered in the acutely psychotic population.

The challenges faced by investigators interested in sex differences in schizophrenia notwithstanding, a clear picture is emerging from what we know about incidence, premorbid functioning, age of onset, symptom severity, long-term outcome and relapse measures, and response to antipsychotic drug treatment which together strongly suggests that women are at an advantage relative to men when it comes to developing and living with schizophrenia. The differences in symptom expression, brain morphology, and functioning, while real, appear most likely to be differences in degree and not in kind. In other words, the preponderance of the literature supports the notion that sex differences exist in the incidence and severity of the *same* illness, with a fair amount of male-typical/female-typical pattern overlap, rather than the development of distinct male vs. female illness subtypes. Because gonadal steroids largely drive sex differences in the brain, attention will now turn to evaluating the evidence for their relationship to the findings of sex differences in schizophrenia.

2 Estrogen in schizophrenia

Women are more vulnerable to psychotic episodes during periods of estrogen withdrawal, including the perimenstrual phase of the menstrual cycle, post-partum, following either abortion or cessation of estrogen therapy, and post-menopause [59–61]. Conversely, reduced relapse rates have been observed for women during pregnancy, when plasma estrogen levels are high [59]. The severity of psychotic symptoms in pre-menopausal women with schizophrenia has actually been shown to fluctuate across the menstrual cycle, with increases in symptom severity associated with low estrogen phases of the cycle [62–65]. Similarly, a negative correlation has been reported between estrogen levels and the therapeutically required dose of antipsychotics in menstruating women [66]. It is not clear whether this last finding is due to estrogen's actions on antipsychotic drug metabolism (discussed above), inherent antipsychotic-like properties of estrogen, or a combination of these mechanisms. In contrast

to these findings, a study conducted among female inpatients with schizophrenia found that estrogen levels, which were measured weekly for one month, were strongly and positively correlated with cognitive function, but did not find evidence for a relationship between hormone levels and psychiatric symptoms in this chronically ill population [67]. The positive relationship between estrogen levels and cognitive function has been replicated in an inpatient population [68]. However, in a study that drew participants from both inpatient and outpatient settings, no relationship was found between estrogen and any measure of cognitive performance, though higher estrogen levels predicted lower positive symptom ratings [69]. Finally, some case reports have indicated that treatment with oral contraceptives *alone* [70, 71] or postmenopausal estrogen replacement therapy [72] can improve psychotic symptoms in women with schizophrenia. Such reports lend credence to the notion that estrogen directly mitigates psychotic symptoms, independent from its potential action on antipsychotic drug metabolism. This idea is also supported by a PET study showing D_2 receptor density fluctuations across menstrual cycle phases in normal women [73] and by a host of animal studies, which have shown that fluctuating estrogen levels impact dopamine neurotransmission and dopamine receptor expression in the brain [74].

If women enjoy a relative level of protection against psychosis because their circulating levels of estradiol are much higher than men's, it is reasonable to ask whether those women who do end up developing schizophrenia are at greater risk in part because for some reason their estradiol levels are abnormally low. This question must be approached with care, because women are usually admitted for a psychotic episode during periods of low estrogen (menstruation, post-partum, post-menopausal). This means that measuring estradiol levels in an acutely psychotic population could suggest a level of gonadal function that is artificially low relative not only to healthy women, but also to the population of women with schizophrenia as a whole. For this reason studies that examine estradiol levels across both high and low points of the menstrual cycle, or across several cycles, are more informative. Riecher-Rossler and colleagues measured hormone levels weekly in 32 women with a history of regular menstrual cycles who were acutely admitted for schizophrenia, for the duration of their hospital stay (range of 3–8 weeks) [63]. They found distinctly reduced plasma estradiol levels relative to the normal population across all phases of the menstrual cycle, as well as muted fluctuations in estradiol levels across the cycle. A similar pattern has been reported for female inpatients with schizophrenia; in this study, all patients showed lower than normal estradiol levels and in fact only one patient showed estradiol levels indicative of normal follicular maturation [67]. In contrast, a recent study found no difference in estradiol levels between female outpatients and normal controls [64]. However, this study was limited to women who met a strict definition for history of regular menstrual cycles, which the previous studies make clear would result in exclusion of many women with the illness.

Hyperprolactinemia is a common consequence of long-term neuroleptic treatment. Hyperprolactinemia occurs because dopamine normally suppresses prolactin secretion from the pituitary, and antipsychotic drugs block the actions of dopamine by antagonizing D_2 receptors in the central nervous system [75]. The neuroleptic-induced increase in prolactin levels is dose-dependent and can reach a level that is two to three times that which is normal [75]. Some second-generation ("atypical") antipsychotics have lower D_2 receptor affinity than conventional neuroleptics and therefore cause a comparatively blunted increase in prolactin secretion or, sometimes, no increase at all [76, 77]. Hyperprolactinemia is a problem for those interested in the role of gonadal steroids in schizophrenia because it leads to hypogonadism in both sexes and amenhorrhea and early menopause in women. For instance in one study, conducted in a mixed population of medicated inpatients and outpatients, upwards of 70% of participants reported irregular menstrual cycles [69]. The side effect of hyperprolactinemia occurs more often in females, and occurs at a lower daily neuroleptic dose [37]. Those interested in gonadal hormone levels associated with the illness itself and not the pharmacological treatment of it can explore this either first episode patients (who do not have a long history of neuroleptic treatment) or those who are being treated with an atypical antipsychotic. The first approach was that taken by Reicher-Rossler et al. who, as discussed above, were still able to find evidence for hypoestrogenism in women with schizophrenia [63]. The second approach was taken by Bergemann and colleagues [78], who tracked serum estrogen and prolactin levels in 75 women diagnosed with schizophrenia. As expected, elevated prolactin levels were found for those taking a typical antipsychotic, but not for those taking an atypical one. Despite this difference, serum estradiol levels were reduced relative to normal reference values in *both* groups over the entire menstrual cycle. Regardless of which drug type was administered, sixty percent of all patients met a strict definition of hypoestrogenism (serum estradiol level less than 30 pg/ml in the follicular phase and less than 100 pg/ml in the periovulatory phase).

The weight of the evidence therefore suggests that women with schizophrenia experience hypoestrogenism, and that this finding is robust independent of neuroleptic-induced endocrine disturbances. Importantly, it remains unknown whether this condition precedes or follows the onset of the illness. Clues to this question come from the work of van Os and colleagues who have reported that peak

bone mass, which is a proxy indicator for cumulative estrogen exposure, is approximately one standard deviation lower in women with schizophrenia at first episode than in control subjects matched for age, education, and other characteristics [79]. This study is important because it shows that very early in the illness course, women with schizophrenia already present with a condition that is indicative of lower lifetime exposure to estrogen. This finding suggests a role for estrogen as a neuroprotective agent during brain development that is conceptually distinct from its acute antipsychotic-like properties. While the available evidence would support the notion that low estrogen levels in some women could tip the balance towards the development of psychopathology, at this time it is still uncertain in which direction the causal arrow points. It remains equally plausible that some illness-associated brain pathology that emerges during development could cause hypogonadism. These possibilities need not be mutually exclusive. For example, an abnormal trajectory of brain development could trigger hypogonadism first, then psychotic symptoms, which are then further exacerbated by the existing low levels of gonadal hormones, and which finally snowball into a full-blown psychiatric illness. The question of whether a low level of circulating estradiol contributes to risk for the illness or is a consequence of the disease process is an important one, but is difficult to disentangle in a clinical population. This highlights the need to explore the involvement of hypothalamic-pituitary-gonadal disruptions and vulnerability to schizophrenia-like phenotypes using animal preparations designed to model the illness.

Finally, in addition to reduced estrogen production by women with schizophrenia, there is evidence that blunted estrogen receptor alpha (ERα) signaling is associated with the illness [80–83]. Thus, the effect of hypoestrogenism on the nervous system of women with schizophrenia is further exacerbated by a reduced ability of the brain to respond to the limited estrogen signal it does receive. Conversely, higher ERα mRNA levels in the prefrontal cortex (pathology of which is a hallmark of schizophrenia), have been correlated with a delayed onset of the illness [82]. This finding is intriguing because it suggests that some measure of protection against hypoestrogenism may be achieved by either a genetic predisposition to express higher levels of the estrogen receptor or by an experience that triggers estrogen receptor upregulation. Both possibilities could be readily tested in an appropriate schizophrenia-relevant animal preparation.

Inspired by the findings of hypoestrogenism in women with schizophrenia and the association between low estrogen levels and the exacerbation of psychotic symptoms, a few prospective clinical studies of estrogen treatment in women of reproductive age with this illness have been undertaken. Kulkarni et al. [84] conducted the first pilot study on an inpatient population, comparing eleven acutely psychotic women receiving adjunctive treatment with ethynylestradiol to seven women who were treated with neuroleptics alone. The adjunctive estradiol group experienced a much more rapid decrease in positive symptoms which was evident as early as 5 days into treatment, though after two months the two groups demonstrated an equivalent improvement in symptoms. These findings supported a role for adjunctive estrogen treatment in the rapid reduction of psychotic symptoms, but because the study was open-label and the sample size was small, the conclusions were tentative. A small (N=24) double-blind, placebo-controlled follow up study by this group provided further support for their preliminary findings. Women receiving adjunctive estradiol treatment in an outpatient setting showed a significantly greater reduction in severe psychotic symptoms compared to women receiving treatment with an antipsychotic alone [85, 86]. In a larger (N=87) randomized, double-blind study in a mostly outpatient population, this group confirmed the beneficial effect of estradiol on psychotic symptoms over a 4 week period [87]. Drawing this time from an inpatient population, Akhondzadeh and colleagues undertook an eight-week, randomized, double-blind, placebo-controlled study of adjunctive estradiol therapy and found that women treated with both estrogen and the typical antipsychotic haloperidol showed greater reductions in both positive and general psychopathology symptoms compared with those who received an antipsychotic without adjunctive estrogen therapy [88]. The composition of the hormone therapy influences the clinical outcome, however. Comparisons between patients receiving adjunctive therapy with conjugated estrogens containing mainly estrone and those not receiving such treatment do not reach the same level of significance as trials in which the therapy is with estradiol [89]. Additionally, significant effects are not observed for either psychopathology or relapse rates following adjunctive treatment in which estradiol is opposed by a progestin [90], although a beneficial effect of this treatment has been reported for measures relevant to thought/language disturbance in schizophrenia [91].

The above studies were conducted in women of reproductive age, but studies among other populations are also supportive of a beneficial role for estrogens in schizophrenia. In a cross-sectional study of postmenopausal women with schizophrenia drawn from an outpatient population, those receiving hormone replacement therapy required a lower average daily antipsychotic dose in order to achieve similar positive symptom ratings as those not receiving hormone therapy. Additionally, they had significantly less severe negative symptoms compared with hormone therapy nonusers, even after controlling for

antipsychotic dose [92]. Findings of a recent pilot study also suggest that adjunctive therapy with the selective estrogen receptor modulator raloxifene hydrochloride results in superior improvement in psychopathology among postmenopausal women with schizophrenia [93]. Finally, a recent double-blind placebo controlled study found that short-term adjunctive treatment with estrogen results in a faster than placebo improvement of symptoms in men with schizophrenia [94].

In summary, it is clear that changing estrogen levels in adult women—whether this is across the natural cycle or in the context of hormone therapy—can influence schizophrenia symptom severity. In particular, the inverse relationship between circulating estradiol levels and psychosis appears especially strong. Metabolism of antipsychotic drugs can also be regulated by estrogen (reviewed by [40]), which may in part explain the impact of estrogen when the hormone is co-administered with a drug. However, as discussed above, support for the relationship between estrogen and psychosis also comes from observations that first episode occurs more often during periods of low estrogen, and that treatment with estrogen therapy alone can provide symptom relief. These observations point to a mechanism of antipsychotic-like action for estrogen that is independent of drug metabolism in adult women. Much less clear is whether hypoestrogenism contributes to risk for the illness by impacting neurodevelopment, or whether it is instead a consequence of the disease process. This question is an important one, but it is difficult to disentangle in a clinical population. Frankly, apart from the work discussed above regarding reduced estrogen-dependent peak bone mass in women with schizophrenia at first episode [79], there is little that amounts to much more than speculation to be found in the literature on this topic. This highlights the need to explore the involvement of hypothalamic-pituitary-gonadal disruptions and vulnerability to schizophrenia-like phenotypes using animal preparations designed to model the illness.

3 Testosterone in schizophrenia

Although interest to date has been in the potential protective role of estrogen in females against schizophrenia, another possible explanation of the earlier age of onset and greater incidence of schizophrenia among males is that testosterone exposure somehow confers risk for the illness. However, the available evidence does not support a role for elevated testosterone in schizophrenia. While in certain circumstances high levels of testosterone have been associated with increases in psychiatric symptoms [95], studies examining circulating testosterone levels in men with schizophrenia actually report either *lower* testosterone levels compared to healthy controls [64, 96–100] or no difference between these groups [101–108]. Levels of the androgen (and testosterone precursor) dehydroepiandrosterone (DHEA) and/or its sulfate conjugate (DHEA-S) are also sometimes evaluated, with somewhat contradictory results; i.e., some studies report lower levels [103, 109], others report equivalent levels [108, 110], and still others report higher levels [106] in male schizophrenic patients compared to healthy controls. Due to the hyperprolactinemia that often follows long-term antipsychotic drug use, studies of gonadal hormone levels may be more informative when conducted in first-episode patients. While one study has reported normal testosterone levels for unmedicated, first episode patients [111], this study was limited in that levels were compared to published norms, not values obtained from a healthy comparison group. Huber and colleagues [112] directly compared gonadal hormone levels among men acutely admitted (for symptom exacerbation or at first episode) to healthy age-matched control men, and found that both testosterone and estrogen levels were significantly lower among the former. Similarly, another study found pre-medicated testosterone levels of men with schizophrenia to be significantly lower compared to healthy control men [113]. Finally, a study published earlier this year reported reduced testosterone levels in a group of male adolescents with prodromal symptoms [114]. Because individuals in this "ultra high risk" group did not yet meet criteria for a psychotic disorder, the finding suggests that reduced testosterone levels may be related to the etiology of psychotic symptoms, rather than emerging as a consequence of the disease process and/or chronic treatment with antipsychotics.

One potential reason for discrepancy in the literature on androgens in schizophrenia is that findings can depend on whether the study population is characterized by severe negative symptoms. Shirayama and colleagues [115] reported a significant negative correlation between negative symptoms and plasma testosterone levels among men with schizophrenia, and that plasma testosterone was significantly lower among those with moderate negative symptoms, compared to controls. However, testosterone levels did not differ between controls and those with low negative symptom ratings. Similarly, another group found that, as a whole, men with schizophrenia did not have lower testosterone levels than healthy matched controls; however, serum testosterone levels were lower than controls among a subgroup with predominantly negative symptoms [116]. This study found no difference between controls and a schizophrenic group characterized by predominantly positive symptoms. This finding appears to be holding up, as other groups have since reported that circulating testosterone levels are negatively correlated with negative symptoms [117], even after controlling for depressive symptoms [118]. In contrast, there appears to be no relationship between negative symptoms and levels of either estradiol or

DHEA-S in men with schizophrenia [115, 118]. Importantly, because both obesity [119] and antipsychotic-induced hyperprolactinemia [37] can lower testosterone levels in men, the study by Ko et al. [118] both excluded obese participants and showed no correlation between prolactin levels and either testosterone levels or negative symptom severity. The relationship only holds for negative symptoms; positive symptoms, treatment reactivity, and cognitive symptoms appear unrelated to testosterone levels [69, 111, 116].

The inverse relationship between testosterone levels and negative symptoms in men with schizophrenia has been supported by the few clinical studies of adjunctive androgen treatment. In a placebo-controlled, randomized double-blind trial, the therapeutic effect of 4 weeks of testosterone augmentation of antipsychotic medication was tested in 30 inpatient men with schizophrenia. Patients treated with testosterone showed significantly greater improvement in negative, but not positive, symptoms, and this effect was still present 2 weeks after discontinuation of hormone treatment [120]. This is the only study to date that has examined adjunctive treatment with testosterone; the remaining studied augmentation with its precursor DHEA. Strous and colleagues [121] found that increases in DHEA and DHEA-S levels were correlated with an improvement in negative symptoms, but not with any improvement in depressive or anxiety symptoms. The notion that the mechanism of action of DHEA in this study was due to its ability to increase testosterone levels is appealing. However a follow-up study by this group reported a modest (though not statistically significant) *decrease* in plasma testosterone levels following DHEA treatment [122]. The upshot is that any effect of DHEA on clinical symptoms of schizophrenia is more likely due to the direct effects of this neuroactive steroid [123] rather than through its conversion to testosterone. While these results imply that studies of adjunctive DHEA treatment may not actually speak to questions regarding the relationship between testosterone and negative symptoms in schizophrenia, the fact that DHEA administration does not appear to alter gonadal hormonal profiles (estrogen levels weren't affected either) bodes well for its continued exploration as adjunctive therapy. Although a more recent study by this group did not find evidence for an impact of DHEA treatment on clinical symptoms, it did report improvement in some cognitive symptoms [124], and another study has reported a reduction in extrapyramidal symptoms that are common side effects of antipsychotic drug therapy [125]. The exploration of androgens as adjunctive therapy in schizophrenia is a field in its infancy, and future work including more studies testing the efficacy of testosterone itself will need to be conducted before a clearer perspective on this question can be gained.

Although limited in number to date, studies examining the relationship between testosterone and schizophrenia are beginning to paint an intriguing picture. Similar to the hypoestrogenism that characterizes women with the illness, men with schizophrenia appear to experience lower than normal levels of circulating testosterone, independent of treatment with antipsychotic medication. Additionally, it seems clear that lower testosterone levels are associated with increased severity of negative symptoms in adult male patients. Once again, however, the question remains whether reduced testosterone levels contribute to illness etiology in men by altering the trajectory of neurodevelopment, or whether the hypogonadism is itself a consequence of the disease process. Indirect support of a role for disrupted testosterone early in development comes from a recent study of 2nd to 4th finger (digit) length ratio (2D:4D), a sexually dimorphic phenotype which has previously been established as a retrospective marker of prenatal testosterone exposure [126]. While there was no difference in mean overall finger lengths between patients with schizophrenia and sex-matched controls, male patients showed significantly greater 2D:4D ratio compared to normal men [127]. Furthermore, men with schizophrenia showed digit ratios similar to normal women. The fact that no group differences existed among females is consistent with the notion that lower prenatal testosterone is only a risk factor for schizophrenia among males—after all, the prenatal environment of females is normally characterized by low levels of testosterone, but women nevertheless enjoy relative protection from the illness. The finding of a demasculinized digit ratio in men with schizophrenia is indeed intriguing, but questions regarding the nature of a (still quite speculative) relationship between hypogonadism and neurodevelopment are difficult to assess in humans. Also, as discussed extensively above, the study of sex differences and sex steroids in schizophrenia is further complicated by a number of factors idiosyncratic to the illness. Our understanding would be greatly enhanced by a preclinical model designed to model known etiological factors in the illness. This nascent field, reviewed below, has not yet been used to gather evidence for or against a relationship for altered gonadal hormones during development and schizophrenia etiology, but interest in this question is growing and the field is reaching the place where clinically relevant hypotheses can now be tested.

4 Sex differences in developmental animal models of schizophrenia

Many frustrations confronted by clinicians studying sex differences and gonadal hormones in schizophrenia (e.g., sampling biases, antipsychotic-induced hyperprolactinemia,

and other factors) are non-issues for the animal researcher. Of course, animal studies aimed at addressing questions in schizophrenia have their own set of issues to be confronted—chief among them, that schizophrenia is a uniquely human illness that cannot be entirely recapitulated by any animal preparation. Further limiting is the fact that many characteristic symptoms, both positive (delusions, hallucinations, and disorganized thinking) and negative (flat affect, impoverished communication) are revealed by patients through language, and of course animals cannot report their experiences to us in this way. The approach of animal researchers then is to focus on phenotypes that both resemble what is observed in people with schizophrenia, and which animals are able to report about through their behavior. Preclinical models of schizophrenia are thus intended to generate animals that show positive-like symptoms such as enhanced response to amphetamine and impaired sensory gating, negative-like symptoms such as disrupted social behavior, and finally cognitive deficits. The development and treatment of neural phenotypes that mediate these behaviors are then explored. The discovery of a post-pubertal emergence of an abnormality is considered to enhance the face validity of the paradigm to schizophrenia, which typically has a late adolescent age of onset. Another aspect that could enhance a paradigm's relevance to the illness would be a greater impact of the treatment/manipulation of interest on males. However, comparisons of relative vulnerability between males and females has generally not yet occurred.

Discussion here will focus on two neurodevelopmental models of schizophrenia in which sex differences in vulnerability have begun to be explored. Because studies of transgenic animals (those in which expression of a schizophrenia-associated gene has been altered) and lesion studies (in which a particular brain area is ablated) typically either include only male subjects or do not treat data from males and females separately, inferences about potential sex-specific effects in these models is not yet possible. Although genetics undoubtedly contributes heavily to illness risk, neurodevelopmental models are relevant because most of the genetic liability for schizophrenia can be accounted for by gene by environment interactions [5]. For a comparison of existing animal models of schizophrenia, many of which (though they have not examined potential sex differences in outcomes) have produced important, clinically relevant findings, the reader is referred to the online Animal Models of Schizophrenia Database, hosted by the Schizophrenia Research Forum at http://www.schizophreniaforum.org/res/models/default.asp.

Example 1: Repeated Variable Prenatal Stress

Maternal stress, malnutrition, and viral infection during pregnancy all increase the risk that the offspring will develop schizophrenia (reviewed by 128). What these risk factors have in common is their ability to activate the hypothalamic-pituitary-adrenal (HPA) axis [128]. It is not known why men are more likely to develop schizophrenia than women, but some epidemiological work suggests that a sex difference in the vulnerability to prenatal stress may be partially accountable [129]. Exposing pregnant female rats to stress results in the production of high levels of circulating glucocorticoids, which readily cross the placenta and act on the developing fetal brain (e.g., [130]). The third week of rodent gestation closely corresponds to the second trimester of human pregnancy, when the fetus is most vulnerable to factors that increase risk for schizophrenia [131]. Maternal stress during the third (but not second) week of rodent gestation, delivered using a repeated variable prenatal stress paradigm, reorganizes the HPA axis, neurodevelopment, and behavior of male offspring in ways that are consistent with the pathology and symptoms of schizophrenia—they exhibit impaired glucocorticoid negative feedback, enhanced sensitivity to amphetamine (which increases brain levels of dopamine), impaired sensory gating, abnormal social behavior, cognitive deficits, increased vulnerability to drug abuse, and altered gene expression in the prefrontal cortex [132–137]. A post-pubertal onset has been demonstrated for several of these phenotypes [133, 134, 137].

Until recently, only male offspring had been characterized in this paradigm. My own work comparing the phenotype of males and females has begun to make it clear that a sex difference exists in the vulnerability to this prenatal insult. Responsiveness to amphetamine is often examined in rodent models of schizophrenia because, in humans, peripheral administration of amphetamine can induce psychotic symptoms in normal individuals and exacerbate them in patients with schizophrenia (reviewed by [138]). In rodents, amphetamine causes a dose-dependent increase in locomotor activity that is mediated by dopaminergic neurotransmission in the nucleus accumbens (e.g., [139]). Enhanced sensitivity to amphetamine is therefore interpreted to indicate excessive mesolimbic dopaminergic transmission, which is considered a key neurochemical disruption mediating the positive symptoms of schizophrenia. Prenatally stressed males show enhanced responsiveness to amphetamine, whereas prenatally stressed females appear indistinguishable from control females [133, 140]. Social behavior is also impacted by exposure to prenatal stress disproportionately in males. When introduced to a novel conspecific, rodents engage in a number of reciprocal investigatory behaviors. In the absence of an anxiogenic phenotype, reduced conspecific investigation can be interpreted as reduced interest in social interaction. Although both sexes show reduced social interaction as a consequence of prenatal stress, the

magnitude of the effect is roughly twice as large in males compared to females [134, 141]. This paradigm thus appears to provide a good model for the finding that men with schizophrenia are more likely than women to exhibit a greater number of and more severe negative symptoms, of which social anhedonia is one [33, 34, 45].

Cognitive disruptions following repeated variable prenatal stress are also more severe in males. In an initial experiment, the object recognition memory of control and prenatally stressed animals of both sexes was tested prior to puberty or during adulthood. Competence on this task, which depends heavily on the perirhinal cortex and, to a certain extent, the prefrontal cortex [142], was found to develop over the peri-adolescent period. The ability of adult males and females to recognize novel objects was found to be essentially equivalent in control animals. However, prenatally stressed males failed to develop competent object recognition memory skills, whereas females' performance on this task was completely unaffected by prenatal stress [137]. This finding demonstrates that a sexually dimorphic response to an environmental risk factor for schizophrenia can occur even for behaviors that do not normally differ between males and females. A separate study found that extinction of a cued fear memory was disrupted in male, but not female rats exposed to prenatal stress, an effect that eliminated the sex difference that is normally observed in this behavior [137]. In rodents, extinction of a cued fear memory is supported by the prefrontal cortex [143]. Because pathophysiology of the prefrontal cortex is a hallmark of schizophrenia, and this brain area undergoes significant sex-specific maturation during the peri-adolescent time frame in both rodents and humans [144–146], the question of whether prefrontal development might be disrupted in a sex-specific fashion by prenatal stress was explored. Using Golgi Cox stained tissue taken from prenatally stressed and control animals of both sexes and multiple postnatal ages, it was found that dendritic maturation of pyramidal neuronal morphology in the prefrontal cortex occurs very late in development, and earlier for females compared to males [135], coincident with their respective timing for puberty. Significantly, peri-adolescent development of dendritic complexity in this region was disrupted by prenatal stress in males, but not females [135]. The pattern of these findings is one of reduced female vulnerability to developing phenotypes related to positive, negative, and cognitive symptoms of schizophrenia in response to an environmental risk factor for schizophrenia, and suggests that the repeated variable prenatal stress paradigm may be a fruitful animal preparation in which to explore mechanisms of sex differences in schizophrenia.

Example 2: Maternal Immune Activation

Maternal infection during pregnancy, due to any number of infectious agents, has been consistently associated with an increased risk of schizophrenia in the offspring (reviewed by [147]). A mechanism common to the immune response is the stimulated release of inflammatory cytokines. Although the immune response also involves stimulation of the HPA axis and release of glucocorticoids, animal models of maternal immune challenge are intended to test the hypothesis that elevated *in utero* exposure to cytokines adversely impacts fetal brain development, resulting in the development of schizophrenia-like neurobehavioral phenotypes. A powerful cytokine-associated inflammatory response can be induced by administration of lipopolysaccharides (LPS; present in the outer membrane of Gram-negative bacteria), polyriboinosinic-polyribocytidilic acid (poly I:C; a viral mimic agent structurally similar to double-stranded RNA), human influenza virus, or the inflammatory cytokine interleukin-6 to pregnant rodents. Offspring born to mothers who were administered an immunogenic agent during gestation show a number of phenotypes relevant to schizophrenia as adults, including impaired sensory gating, enhanced sensitivity to amphetamine and other evidence of subcortical hyperdopaminergia, reduced social interaction, some cognitive deficits, and altered development of both hippocampus and prefrontal cortex (reviewed by [148, 149]).

Limited investigation of sex differences in models of maternal immune activation has been conducted, but the results to date are intriguing. A consistent outcome of prenatal LPS exposure is impaired prepulse inhibition (PPI) of the auditory startle response [150–152], which refers to the ability of a non-startling prestimulus or "prepulse" to inhibit an individual's response to a stimulus that would otherwise normally induce a startle. The use of this measure of sensory gating in animal models of schizophrenia is extremely attractive because it can be tested using essentially identical methods in rodents and humans [153, 154]. A deficit in PPI has been repeatedly described for individuals with schizophrenia and for normal individuals experimentally treated with amphetamine; in patients the deficit is ameliorated by antipsychotic drugs (reviewed by [155]), which primarily treat positive symptoms of the illness. When the effect of prenatal LPS on PPI was compared between the sexes at multiple post-pubertal ages, it was found that the deficit in sensory gating developed earlier and was more severe in prenatal LPS-exposed males compared to females [152, 156]. The earlier PPI disruption in LPS-exposed males resembles the earlier age of onset that is observed for men as compared to women with schizophrenia, and the sex difference in severity is mirrored in the finding that women with schizophrenia are less likely to show PPI deficits (relative to healthy controls of the same sex) than are men [157]. Follow-up experiments in this animal model might therefore be useful in testing the potential protective role for estrogen against phenotypes related to psychosis.

Unlike what is observed for the animal preparations discussed so far, the response to prenatal exposure to poly I:C appears to be largely comparable between male and female offspring of poly I:C treated mothers—the sexes are equivalently hypersensitive to amphetamine, and show PPI deficits and cognitive impairments of a similar magnitude [158, 159]. A sexually dimorphic response has been observed for only a few phenotypes. For example, male but not female offspring show an increase in tyrosine hydroxylase (an enzyme crucial for dopamine synthesis) in the striatum, a reduction in dopamine receptors in the prefrontal cortex, and impaired contextual fear conditioning [159, 160]. On the other hand, this same group found that only female offspring born to poly I:C treated mothers showed a reduced ability to learn the predictive relationship between an auditory tone and a fearful stimulus (cued fear conditioning) [160]. Since maternal immune activation occurs following both LPS and poly I:C treatment, differences in the pattern of effects between the two paradigms are most likely due to the fact the prenatal LPS experiments discussed above were conducted in rats, whereas the potential sex-specific impact of prenatal poly I:C treatment has only been examined to date in mice. Thus it is possible that rats are better suited to model sex-specific vulnerability in response to maternal immune activation.

5 Gonadal hormones and animal phenotypes relevant to schizophrenia

To date, the role of estrogen and/or testosterone in mediating neurobehavioral sex differences has not been examined within the context of animal models of schizophrenia—as the above discussion makes clear, the field is just beginning to describe sex differences in these models, and has not begun to address the question of which mechanism(s) underlie the development of these differences. However, a wealth of research conducting in animals does point to a role for gonadal steroids in the expression of these phenotypes. A large body of work has demonstrated that gonadal steroids exert a profound "organizational" impact on brain development during the perinatal and early postnatal stages, when sexual differentiation of brain areas involved in the control of reproductive behaviors is occurring (see [161]). Gonadal hormones during this early sensitive period organize the brain to allow for later sex-specific "activational" effects during adulthood. It is outside the scope of this review to exhaustively treat this body of work; rather, the focus here will first be on the potential late organizational impact of gonadal steroids during adolescent brain development, because the typical age of onset for schizophrenia is late adolescence and because the greater male vulnerability in animal models of the illness (reviewed above) similarly emerges after puberty. These studies are most relevant to the hypothesis that gonadal steroids may contribute to the development of schizophrenia by influencing brain development. Secondly, activational effects of gonadal steroids on rodent behaviors particularly relevant to schizophrenia will be highlighted. These latter studies are most relevant to the hypothesis that gonadal steroids modulate symptom expression in individuals with schizophrenia.

5.1 Pubertal hormones may organize brain development during adolescence

A small but growing body of literature suggests that, in addition to the organizational impact of gonadal steroids during early development and the activational impact they have during adulthood, a period of late organization may occur during adolescence in response to the pubertal surge of gonadal hormones (reviewed by [162]). The structures that stand to be most affected by pubertal hormones are those whose development is ongoing during adolescence, such as the cerebral cortex, hippocampus, and amygdala. Importantly, these are some of the primary areas implicated in the pathophysiology of schizophrenia [163, 164].

Longitudinal pediatric neuroimaging studies have revealed that numerous brain areas undergo sex-specific patterns of maturation during human adolescence. Total brain volume is greater in males compared to females and does not dramatically change after age five; however, there is a shift in the relative volume of gray and white matter [146, 165]. Whereas cortical white matter continues to increase in a linear fashion over adolescence, with steeper increases in boys compared to girls, cortical gray matter undergoes a region-specific, nonlinear pattern of development [146, 165]. Gray matter in most regions shows an inverted U-shaped trajectory, with pre-adolescent increases followed by post-adolescent decreases [146, 165]. Peak volumes occur 1–2 years earlier in girls compared to boys, consistent with their average age difference at puberty. Although the shapes of gray matter trajectories are region-specific, females reach peak volume earlier in all regions. Interestingly, it is the shape of the developmental trajectory, and not absolute cortical thickness itself, which best predicts intellectual ability [166]. Very intelligent children show the most rapid rates of cortical thickening and thinning, compared to those with above average or average intelligence [166]. The trajectory of the prefrontal cortex shows the greatest correlation to intelligence [166, 167], and differences between the adolescent and adult gray matter volumes are greatest in the prefrontal cortex [145]. Subcortical structures also show sex-specific patterns of development over adolescence. Similar to frontal gray matter, the caudate nucleus follows an inverted U-shaped

trajectory of maturation, with the peak volume occurring earlier for girls [165]. A cross sectional study of children ages 4–18 showed steeper increases in amygdala size for males, whereas the hippocampus grew more quickly in females [168]. While these findings are certainly suggestive of sex-specific maturation of limbic structures over adolescence, they need to be replicated using a longitudinal study design. Some studies have attempted to relate individual differences in testosterone levels to cortical anatomy, but the use of cross-sectional designs and/or the statistical combination of data from males and females has precluded inferences about whether androgen signaling is involved in sex-specific patterns of cortical maturation. Very recently, Giedd and colleagues have employed a longitudinal study design to demonstrate greater masculinization of cortical maturation *during adolescence* in individuals carrying an allele associated with more efficient functioning of the androgen receptor [169]. This is the best evidence to date indicating that sex steroids shape sex-specific brain development in humans during adolescence.

The *in vivo* neuroimaging studies discussed above have provided considerable evidence that the human brain follows sex- and region-specific patterns of volume maturation over adolescence. However, there are methodological and ethical limitations to the ways in which hypotheses about gonadal hormone involvement in this process can be tested in humans. Additionally, neuroimaging studies cannot speak to the cellular underpinnings of the observed changes in volume. This is where an animal model could be extremely useful, provided similar developmental patterns could be established in another species. Fortunately, the evidence available to date indicates that the rodent provides an excellent model for the sex-specific, peri-adolescent development of the brain, and goes one step further by implicating pubertal exposure to either estrogen or testosterone, depending on the brain region. This literature has been elegantly reviewed elsewhere [162], so discussion here will focus on brain areas and behaviors most relevant to schizophrenia.

Just like the human cortex, the rat cerebral cortex is sexually dimorphic, with males having larger volumes than females [170]. Similar to the prefrontal cortex of humans, the rat prefrontal cortex undergoes a post-adolescent reduction in gray matter volume, which is due to a region-specific loss of neurons. Neuronal loss occurs in both sexes but to a greater extent in females [144]. Neuronal apoptosis in the cortex during adolescence is driven by exposure to ovarian hormones, as females who are ovariectomized just prior to puberty have the same number of neurons in adulthood as males, whereas neuron number is unaltered in males gonadectomized prior to puberty [171]. Meanwhile, over the same period of time, prefrontal neurons undergo a dramatic period of sex-specific growth and synaptic refinement. Maturation of pyramidal neuron dendritic complexity in the prefrontal cortex occurs earlier for females compared to males, coincident with their respective timing for puberty [135]. Dendritic spine density on these neurons increases prior to puberty; following puberty, some spine populations undergo pruning whereas others do not [135]. In contrast to gray matter, frontal white matter continues to increase in a linear fashion over the peri-adolescent time frame [144]. Just as in humans, this increase is greater in males compared to females. In the corpus callosum, where axonal composition can more easily be quantified, it has been shown that peri-adolescent changes in size reflect overlapping processes of myelination and axonal pruning, though adult sex differences in callosal size reflect differences in myelination rather than total axon number [172]. Again, it appears to be pubertal exposure to ovarian hormones that drives this adult sex difference, as females ovariectomized prior to puberty have more myelinated axons than intact females, while groups did not differ in total number of axons [173]. Finally, other structures that show pathology in schizophrenia besides the cerebral cortex are also refined during normal adolescence in animal models. For instance, the basolateral nucleus of the amygdala undergoes significant neuronal and glial loss between adolescence and adulthood [174], and dendritic maturation there follows a sex-specific pattern over the peri-adolescent time frame [175]. In the medial amygdala, dendritic pruning accompanies the addition of new cells during adolescence [176, 177]. In this case, pre-pubertal gonadectomy in males reduces the peri-pubertal addition of new cells to this region and abolishes the male advantage in its adult size, whereas pre-pubertal ovariectomy is without effect [177]. In the hippocampus, dendritic spine density increases around the onset of puberty and then undergoes pruning thereafter; this process is also driven by testosterone because pre-pubertal gonadectomy prevents the refinement in spines from occurring [178]. Thus, quantitative neuroanatomical work in the rat indicates that changes observed in regional brain volume over human adolescence are likely due to a combination of cellular events including late waves of neuronal apoptosis and cell genesis, as well as continued myelination, dendritic ramification, and synaptic refinement. Additionally, these animal studies strongly suggest that the volumetric changes observed the human cerebral cortex may be influenced by gonadal steroids at the time of puberty.

Peri-adolescent, sex-specific changes in the brain are by no means limited to gross structure and neuronal morphology. In particular, dopamine neurotransmission—considered to be highly relevant to schizophrenia given the mechanism of antipsychotic drug action—matures during adolescence in a region-specific fashion. In both

the prefrontal cortex and striatum, dopamine receptors first show increased expression followed by a gradual reduction in expression during late adolescence [179, 180]. In the nucleus accumbens, dopamine receptors also increase at puberty, but remain stable thereafter [179]. In the striatum, changes in receptor expression are more dramatic in males compared to females [181], but are not altered by pre-pubertal gonadectomy in males or pre-pubertal ovariectomy in females suggesting that pubertal hormones are not instrumental in establishing adult levels of dopamine receptors in this area [182]. However, it remains to be seen whether dopamine receptor overproduction and pruning in the prefrontal cortex is sexually dimorphic and if so, whether there is a role for gonadal hormones in this process. In addition to changes in receptors for the neurotransmitter, dopaminergic innervation to the prefrontal cortex continues through adolescence [183], and there is increased interaction between dopamine-containing fibers and inhibitory neurons [184]. Finally, dopamine facilitation of glutamate responses in the prefrontal cortex is known to be refined during adolescence [185–187]. At the same time that dopamine fibers are innervating the prefrontal cortex, reciprocal connections between this area and the basolateral amygdala are being remodeled, which are accompanied by adolescent changes in the expression of genes involved in both synaptic plasticity and, suggestively, steroid metabolism [188, 189]. Especially given the sex differences known to exist in the subcortical dopamine system [e.g., 190], examination of sex differences in these processes and the potential role for pubertal hormones in them should be examined.

What are the functional consequences of this dynamic remodeling of the adolescent brain? Under normal circumstances, it seems clear that these processes serve to fine-tune behaviors that are necessary for adult members of a species to survive and to thrive. In addition to the influence of pubertal hormones on the maturation of sexual behaviors, which will not be discussed here, testicular hormones during adolescence promote the development of male-typical adult social behaviors in rodents [191–194]. In at least some cases, ovarian hormones during adolescence actively suppress the development of these behaviors [193]. Additionally, anxiety-related behaviors appear to be organized by peri-adolescent exposure to testosterone; for instance, pre-pubertal castration abolishes the adult sex difference in open field ambulation, a measure of how anxiogenic a novel environment is for a rodent [195]. Along similar lines, the ability of a novel (more anxiogenic) environment to reduce social interactions between male rodents develops over puberty, and is prevented in animals that are castrated prior to puberty [196]. Testosterone replacement during puberty, but not during adulthood, will rescue this effect [196].

The ability of pubertal gonadal steroids to organize cognitive ability has also been hypothesized, on the basis of findings that many cognitive abilities do not mature until after puberty in both rodents and humans, and that sexually dimorphic cognitive styles do not emerge until after puberty [137, 197, 198]. Interestingly, one study found that men with idiopathic hypogonadotropic hypogonadism (IHH), who experienced abnormally low levels of gonadal steroids during adolescence, showed impaired spatial cognition as adults compared to both healthy controls and to men who developed the same condition as adults [199]. Such findings hint at a possible relationship between exposure to gonadal steroids during adolescence and the development of adult cognitive abilities. Recently, my laboratory has directly tested this relationship using a fear conditioning paradigm in rats. The extinction of a discrete cue-associated fear memory is sexually dimorphic in rats, with males readily learning to extinguish responses to a stimulus (auditory tone) that no longer predicts a fearful event (mild footshock), whereas females continue to respond to the stimulus even in the absence of the fearful event [137]. Females deprived of ovarian hormones during adolescence showed the male-typical pattern of extinction learning, whereas males deprived of testicular hormones during adolescence showed the female-typical pattern [200]. Extinction of discrete cue-associated conditioned fear memory is highly dependent on the ventral medial prefrontal cortex (e.g., [201]). Therefore, the findings of this study indicate that exposure to gonadal steroids during adolescence can organize prefrontal-dependent cognition, which is disrupted in schizophrenia.

The evidence reviewed above makes a compelling case that pubertal hormones can organize brain structures, neurotransmitter systems, and behaviors that exhibit well-known pathology in schizophrenia. Such findings encourage the notion that adolescent exposure to gonadal hormones (and/or disruptions in this process) may be involved in the development of schizophrenia and in sex differences in its incidence. At this point such a notion is purely speculative; however, since animal models have recently described post-pubertal emergence of sex differences in the vulnerability to insults known to increase risk for this illness, translational science is now poised to directly test this hypothesis (see Table 1).

5.2 Activational effects on schizophrenia-relevant animal behaviors

Distinct from their role in neurodevelopment, during adulthood gonadal steroids modulate rodent behaviors that are relevant to schizophrenia. These findings are most relevant to the hypothesis that gonadal steroids modulate symptom expression in individuals with schizophrenia. For

Table 1 Summary of major sex differences and the impact of sex steroids in schizophrenia. Similar findings generated in preclinical paradigms are also shown. The ? symbol denotes an area remaining to be explored in animal preparations intended to model schizophrenia. Please refer to the text for references. E (estrogen), T (testosterone), PPI (prepulse inhibition of the startle response), LPS (lipopolysaccharide), RVPS (repeated variable prenatal stress), poly I:C (polyinosinic:polycytidylic acid), PFC (prefrontal cortex)

Measure in Schizophrenia	Direction of Effect	Preclinical Parallel
Incidence	males > females by ~40%	n/a
Age of Peak Onset	post-pubertal + earlier in males	Prenatal LPS: PPI
Late Onset	females; post-menopausal	?
Response to Antipsychotic Drugs	Male < Female	?
Negative Symptoms	Male > Female	RVPS: social investigation
Cognitive Deficits	Male > Female	RVPS: object recognition memory + extinction of fear memory; Prenatal Poly I:C: fear conditioning
Vulnerability to Substance Abuse	Male > Female	?
Brain Morphological Changes	Male > Female	RVPS: PFC dendritic development
Gonadal Hormone Levels	↓ E in Females, ↓ T in Males	?
	Impact of Gonadal Steroids	
Positive Symptoms	↓ by estrogen	?
Response to Neuroleptics	↑ by estrogen	?
Cognitive Functioning	↑ by estrogen	?
Negative Symptoms	↓ by testosterone	?

instance, numerous studies have demonstrated a role for estrogen in behaviors that may be related to the subcortical hyperdopaminergic state observed in schizophrenia. Estrogen enhances PPI in ovariectomized female rats, and prevents PPI deficits induced by drugs that can disrupt sensory gating [202]. Similar findings have also been reported in healthy women [203]. Latent inhibition (LI) is a selective attention paradigm that measures an individual's propensity to ignore irrelevant stimuli, and considerable experimental evidence supports the conclusion that disrupted LI is related to subcortical hyperdopaminergia (reviewed by [204]). In most studies (though not all [205]), LI is disrupted by ovariectomy and estrogen treatment mimics the rescuing impact of antipsychotic drug treatment on this behavior [206, 207]. These findings could be due to an endogenous neuroleptic-like activity of estrogen; indeed, numerous studies suggest that estrogen acts at multiple levels to reduce subcortical dopamine activity, which is hypothesized to be elevated in schizophrenia [74, 208–212]. On the other hand, in healthy subject populations, PPI is reduced in women compared to men, and estrogen is implicated in this sex difference because PPI is lowest during the midluteal phase of the menstrual cycle, when estrogen levels are high [213, 214]. Similarly, PPI fluctuates across the rat estrous cycle, with the lowest amount demonstrated during proestrus, when estrogen levels are highest [215]. The resolution of these apparently conflicting findings probably lies in the fact that estrogen's impact on the dopamine system is both timing- and dose-dependent; for instance, estrogen reduces stimulated dopamine release in the striatum at high doses or following prolonged exposure, but enhances it at low doses (e.g., [74, 216]). Thus although a clear role for estrogen exists, it is difficult to make broad statements regarding the direction of its effect on the subcortical dopamine system; in contrast, the rodent work has made it fairly clear that sex differences in this system are not impacted by testicular hormones in males (reviewed by [190]).

The behavioral measures examined in the above studies are most closely related to the symptoms of schizophrenia that are effectively treated with antipsychotics; however, schizophrenia is a multi-faceted illness, leaving open the possibility that androgens could impact behaviors with greater relevance to negative symptoms, which are more commonly observed in male patients. Indeed, in rodent paradigms of social investigation, males engage in more social investigation than females [217], and in this case the sex difference relies on circulating testosterone—males castrated as adults behave similarly to intact females, and testosterone administration (whether to castrated males or adult females) results in levels of investigation seen in intact males [218, 219]. Because this pattern resembles the inverse relationship found between testosterone levels and negative symptoms among men with schizophrenia (see above), the possibility that reduced testosterone mediates the social anhedonia observed in some rodent models of schizophrenia should be tested.

Finally, the relationship between gonadal steroids and cognitive measures in rodents is heavily researched but

highly nuanced. Both sex differences and an influence of gonadal steroids have been described for nearly every rodent cognitive measure, including those disrupted in the animal preparations discussed above, i.e., object recognition memory, spatial memory, working memory, and fear conditioning (reviewed by [220]). However, both the presence and direction of the effects depend on methodological factors, including the amount of stress involved in the task, the species and strain of animals used, and the steroid dose administered (e.g., [220, 221]). Therefore, the impact of sex steroids on cognitive outcomes in animal models of schizophrenia will need to be evaluated within the context of carefully designed paradigms in order to allow more generalizable conclusions to be made.

6 Conclusions

In summary, schizophrenia is a neuropsychiatric illness that appears to disproportionately affect men. Men are approximately 40% more likely to develop the illness compared to women. Men have a well-documented earlier age of onset, as well as poorer premorbid adjustment, more severe illness course, more negative symptoms, poorer response to antipsychotic drug therapy, and possibly greater ventricular enlargement and cortical atrophy. In women, estrogen is associated with relief from psychotic symptoms of the illness, and the protective role of estrogen is highlighted by the later age of adolescent onset and second postmenopausal peak in incidence observed for women, as well as the finding that women who do develop schizophrenia have lower levels of circulating estrogens. Similarly, men with schizophrenia have lower levels of testosterone, and there is an inverse relationship between testosterone levels and severity of negative symptoms. The evidence from first-episode and unmedicated patients indicates that the hypogonadism observed in patients with schizophrenia often occurs independently of neuroleptic-induced endocrine disturbances; however it remains unknown whether this condition is of etiological relevance. Gonadal steroids have clearly been demonstrated to modulate schizophrenia symptom severity; however, evidence for this relationship should be considered separately from the hypothesis that gonadal steroids impact neurodevelopment to tip the balance towards or against development of psychopathology. Preclinical models of schizophrenia have recently begun to describe a pattern of post-pubertal emergence of enhanced male vulnerability to insults known to increase risk for schizophrenia, including prenatal stress and maternal immune activation. Additional animal work has established that gonadal steroids exert both organizational and activational influences on neural and behavioral phenotypes relevant to schizophrenia, though this has yet to be meaningfully explored in the context of preclinical models of schizophrenia. The hope is that these models can now be exploited to provide insight about how early life insults contribute to risk for schizophrenia, whether there might be a role for the pubertal rise in gonadal steroids in the generation of phenotypes associated with schizophrenia, and, ultimately, to elucidate the neural mechanisms underlying enhanced male vulnerability to the illness.

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References

1. Seeman MV. Psychopathology in women and men: focus on female hormones. Am J Psychiatry. 1997;154(12):1641–7.
2. Buchanan RW, Carpenter WT. Domains of psychopathology: an approach to the reduction of heterogeneity in schizophrenia. J Nerv Ment Dis. 1994;182(4):193–204.
3. Saha S, Chant D, Welham J, McGrath J. A systematic review of the prevalence of schizophrenia. PLoS Med. 2005;2(5):e141.
4. Tsuang M. Schizophrenia: genes and environment. Biol Psychiatry. 2000;47(3):210–20.
5. van Os J, Rutten BP, Poulton R. Gene-environment interactions in schizophrenia: review of epidemiological findings and future directions. Schizophr Bull. 2008;34(6):1066–82.
6. Marenco S, Weinberger DR. The neurodevelopmental hypothesis of schizophrenia: following a trail of evidence from cradle to grave. Dev Psychopathol. 2000;12(3):501–27.
7. Kraepelin E. Psychiatrie. Leipzig: Barth; 1909.
8. Angermeyer MC, Kuhn L. Gender differences in age at onset of schizophrenia. An overview. Eur Arch Psychiatry Neurol Sci. 1988;237(6):351–64.
9. Hafner H, Riecher A, Maurer K, Loffler W, Munk-Jorgensen P, Stromgren E. How does gender influence age at first hospitalization for schizophrenia? A transnational case register study. Psychol Med. 1989;19(4):903–18.
10. Hafner H, Behrens S, De Vry J, Gattaz WF. Oestradiol enhances the vulnerability threshold for schizophrenia in women by an early effect on dopaminergic neurotransmission. Evidence from an epidemiological study and from animal experiments. Eur Arch Psychiatry Clin Neurosci. 1991;241(1):65–8.
11. Hambrecht M, Maurer K, Hafner H. Gender differences in schizophrenia in three cultures. Results of the who collaborative study on psychiatric disability. Soc Psychiatry Psychiatr Epidemiol. 1992;27(3):117–21.
12. Hafner H, Riecher-Rossler A, Maurer K, Fatkenheuer B, Loffler W. First onset and early symptomatology of schizophrenia. A chapter of epidemiological and neurobiological research into age and sex differences. Eur Arch Psychiatry Clin Neurosci. 1992;242(2–3):109–18.
13. Hafner H, an der Heiden W, Behrens S, Gattaz WF, Hambrecht M, Loffler W, et al. Causes and consequences of the gender difference in age at onset of schizophrenia. Schizophr Bull. 1998;24(1):99–113.
14. Hafner H, Riecher-Rossler A, An Der Heiden W, Maurer K, Fatkenheuer B, Loffler W. Generating and testing a causal

explanation of the gender difference in age at first onset of schizophrenia. Psychol Med. 1993;23(4):925–40.
15. Hafner H, Maurer K, Loffler W, Riecher-Rossler A. The influence of age and sex on the onset and early course of schizophrenia. Br J Psychiatry. 1993;162:80–6.
16. Munk-Jorgensen P. First-admission rates and marital status of schizophrenics. Acta Psychiatr Scand. 1987;76(2):210–6.
17. Konnecke R, Hafner H, Maurer K, Loffler W, an der Heiden W. Main risk factors for schizophrenia: Increased familial loading and pre- and peri-natal complications antagonize the protective effect of oestrogen in women. Schizophr Res. 2000;44 (1):81–93.
18. Albus M, Maier W. Lack of gender differences in age at onset in familial schizophrenia. Schizophr Res. 1995;18(1):51–7.
19. Cohen RZ, Seeman MV, Gotowiec A, Kopala L. Earlier puberty as a predictor of later onset of schizophrenia in women. Am J Psychiatry. 1999;156(7):1059–64.
20. Castle DJ, Phelan M, Wessely S, Murray RM. Which patients with non-affective functional psychosis are not admitted at first psychiatric contact? Br J Psychiatry. 1994;165(1):101–6.
21. Schwartz JE, Fennig S, Tanenberg-Karant M, Carlson G, Craig T, Galambos N, et al. Congruence of diagnoses 2 years after a first-admission diagnosis of psychosis. Arch Gen Psychiatry. 2000;57(6):593–600.
22. Aleman A, Kahn RS, Selten JP. Sex differences in the risk of schizophrenia: evidence from meta-analysis. Arch Gen Psychiatry. 2003;60(6):565–71.
23. McGrath J, Saha S, Welham J, El Saadi O, MacCauley C, Chant D. A systematic review of the incidence of schizophrenia: the distribution of rates and the influence of sex, urbanicity, migrant status and methodology. BMC Med. 2004;2:13.
24. Hafner H, Maurer K, Loffler W, Fatkenheuer B, an der Heiden W, Riecher-Rossler A, et al. The epidemiology of early schizophrenia. Influence of age and gender on onset and early course. Br J Psychiatry. 1994;23:29–38.
25. Hafner H, Maurer K, Loffler W, an der Heiden W, Munk-Jorgensen P, Hambrecht M, et al. The abc schizophrenia study: a preliminary overview of the results. Soc Psychiatry Psychiatr Epidemiol. 1998;33(8):380–6.
26. Zigler E, Glick M, Marsh A. Premorbid social competence and outcome among schizophrenic and nonschizophrenic patients. J Nerv Ment Dis. 1979;167(8):478–83.
27. Larsen TK, McGlashan TH, Johannessen JO, Vibe-Hansen L. First-episode schizophrenia: Ii. Premorbid patterns by gender. Schizophr Bull. 1996;22(2):257–69.
28. Angermeyer MC, Goldstein JM, Kuehn L. Gender differences in schizophrenia: rehospitalization and community survival. Psychol Med. 1989;19(2):365–82.
29. Shepherd M, Watt D, Falloon I, Smeeton N. The natural history of schizophrenia: A five-year follow-up study of outcome and prediction in a representative sample of schizophrenics. Psychol Med Monogr Suppl. 1989;15:1–46.
30. Salokangas RK. Prognostic implications of the sex of schizophrenic patients. Br J Psychiatry. 1983;142:145–51.
31. Seeman MV. Current outcome in schizophrenia: women vs men. Acta Psychiatr Scand. 1986;73(6):609–17.
32. Grossman LS, Harrow M, Rosen C, Faull R, Strauss GP. Sex differences in schizophrenia and other psychotic disorders: a 20-year longitudinal study of psychosis and recovery. Compr Psychiatry. 2008;49(6):523–9.
33. Shtasel DL, Gur RE, Gallacher F, Heimberg C, Gur RC. Gender differences in the clinical expression of schizophrenia. Schizophr Res. 1992;7(3):225–31.
34. Gur RE, Petty RG, Turetsky BI, Gur RC. Schizophrenia throughout life: sex differences in severity and profile of symptoms. Schizophr Res. 1996;21(1):1–12.
35. Meltzer HY, Busch DA, Fang VS. Serum neuroleptic and prolactin levels in schizophrenic patients and clinical response. Psychiatry Res. 1983;9(4):271–83.
36. Bowers Jr MB, Swigar ME, Jatlow PI, Goicoechea N. Plasma catecholamine metabolites and early response to haloperidol. J Clin Psychiatry. 1984;45(6):248–51.
37. Melkersson KI, Hulting AL, Rane AJ. Dose requirement and prolactin elevation of antipsychotics in male and female patients with schizophrenia or related psychoses. Br J Clin Pharmacol. 2001;51(4):317–24.
38. Carrillo JA, Benitez J. Cyp1a2 activity, gender and smoking, as variables influencing the toxicity of caffeine. Br J Clin Pharmacol. 1996;41(6):605–8.
39. Kelly DL, Conley RR, Tamminga CA. Differential olanzapine plasma concentrations by sex in a fixed-dose study. Schizophr Res. 1999;40(2):101–4.
40. Tanaka E. Gender-related differences in pharmacokinetics and their clinical significance. J Clin Pharm Ther. 1999;24 (5):339–46.
41. DeLisi LE. The significance of age of onset for schizophrenia. Schizophr Bull. 1992;18(2):209–15.
42. Andia AM, Zisook S, Heaton RK, Hesselink J, Jernigan T, Kuck J, et al. Gender differences in schizophrenia. J Nerv Ment Dis. 1995;183(8):522–8.
43. Grossman LS, Harrow M, Rosen C, Faull R. Sex differences in outcome and recovery for schizophrenia and other psychotic and nonpsychotic disorders. Psychiatric Services (Washington, DC). 2006;57(6):844–50.
44. Bottlender R, Jager M, Groll C, Strauss A, Moller HJ. Deficit states in schizophrenia and their association with the length of illness and gender. Eur Arch Psychiatry Clin Neurosci. 2001;251 (6):272–8.
45. Goldstein JM, Link BG. Gender and the expression of schizophrenia. J Psychiatr Res. 1988;22(2):141–55.
46. Willhite RK, Niendam TA, Bearden CE, Zinberg J, O'Brien MP, Cannon TD. Gender differences in symptoms, functioning and social support in patients at ultra-high risk for developing a psychotic disorder. Schizophr Res. 2008;104(1–3):237–45.
47. McGlashan TH, Bardenstein KK. Gender differences in affective, schizoaffective, and schizophrenic disorders. Schizophr Bull. 1990;16(2):319–29.
48. Seidman LJ, Goldstein JM, Goodman JM, Koren D, Turner WM, Faraone SV, et al. Sex differences in olfactory identification and wisconsin card sorting performance in schizophrenia: Relationship to attention and verbal ability. Biol Psychiatry. 1997;42 (2):104–15.
49. Goldstein JM, Seidman LJ, Goodman JM, Koren D, Lee H, Weintraub S, et al. Are there sex differences in neuropsychological functions among patients with schizophrenia? Am J Psychiatry. 1998;155(10):1358–64.
50. Walder DJ, Seidman LJ, Cullen N, Su J, Tsuang MT, Goldstein JM. Sex differences in language dysfunction in schizophrenia. Am J Psychiatry. 2006;163(3):470–7.
51. Nopoulos P, Flaum M, Andreasen NC. Sex differences in brain morphology in schizophrenia. Am J Psychiatry. 1997;154 (12):1648–54.
52. Andreasen NC, Swayze 2nd VW, Flaum M, Yates WR, Arndt S, McChesney C. Ventricular enlargement in schizophrenia evaluated with computed tomographic scanning. Effects of gender, age, and stage of illness. Arch Gen Psychiatry. 1990;47 (11):1008–15.
53. Goldberg TE, Gold JM, Torrey EF, Weinberger DR. Lack of sex differences in the neuropsychological performance of patients with schizophrenia. Am J Psychiatry. 1995;152(6):883–8.
54. Hoff AL, Wieneke M, Faustman WO, Horon R, Sakuma M, Blankfeld H, et al. Sex differences in neuropsychological

functioning of first-episode and chronically ill schizophrenic patients. Am J Psychiatry. 1998;155(10):1437–9.
55. Gur RE, Mozley PD, Shtasel DL, Cannon TD, Gallacher F, Turetsky B, et al. Clinical subtypes of schizophrenia: differences in brain and csf volume. Am J Psychiatry. 1994;151(3):343–50.
56. Lewine RR, Walker EF, Shurett R, Caudle J, Haden C. Sex differences in neuropsychological functioning among schizophrenic patients. Am J Psychiatry. 1996;153(9):1178–84.
57. Walker EF, Lewine RR. Sampling biases in studies of gender and schizophrenia. Schizophr Bull. 1993;19(1):1–7. discussion 9–14.
58. Goldstein JM. Sampling biases in studies of gender and schizophrenia: a reply. Schizophr Bull. 1993;19(1):9–14.
59. Kendell RE, Chalmers JC, Platz C. Epidemiology of puerperal psychoses. Br J Psychiatry. 1987;150:662–73.
60. Mahe V, Dumaine A. Oestrogen withdrawal associated psychoses. Acta Psychiatr Scand. 2001;104(5):323–31.
61. Bergemann N, Parzer P, Nagl I, Salbach B, Runnebaum B, Mundt C, et al. Acute psychiatric admission and menstrual cycle phase in women with schizophrenia. Arch Wom Ment Health. 2002;5(3):119–26.
62. Hallonquist JD, Seeman MV, Lang M, Rector NA. Variation in symptom severity over the menstrual cycle of schizophrenics. Biol Psychiatry. 1993;33(3):207–9.
63. Riecher-Rossler A, Hafner H, Stumbaum M, Maurer K, Schmidt R. Can estradiol modulate schizophrenic symptomatology? Schizophr Bull. 1994;20(1):203–14.
64. Rubin LH, Carter CS, Drogos L, Pournajafi-Nazarloo H, Sweeney JA, Maki PM. Peripheral oxytocin is associated with reduced symptom severity in schizophrenia. Schizophr Res. 2010;124(1–3):13–21.
65. Bergemann N, Parzer P, Runnebaum B, Resch F, Mundt C. Estrogen, menstrual cycle phases, and psychopathology in women suffering from schizophrenia. Psychol Med. 2007;37 (10):1427–36.
66. Gattaz WF, Vogel P, Riecher-Rossler A, Soddu G. Influence of the menstrual cycle phase on the therapeutic response in schizophrenia. Biol Psychiatry. 1994;36(2):137–9.
67. Hoff AL, Kremen WS, Wieneke MH, Lauriello J, Blankfeld HM, Faustman WO, et al. Association of estrogen levels with neuropsychological performance in women with schizophrenia. Am J Psychiatry. 2001;158(7):1134–9.
68. Ko YH, Joe SH, Cho W, Park JH, Lee JJ, Jung IK, et al. Estrogen, cognitive function and negative symptoms in female schizophrenia. Neuropsychobiology. 2006;53(4):169–75.
69. Halari R, Kumari V, Mehrotra R, Wheeler M, Hines M, Sharma T. The relationship of sex hormones and cortisol with cognitive functioning in schizophrenia. J Psychopharmacology Oxf Engl. 2004;18(3):366–74.
70. Felthous AR, Robinson DB, Conroy RW. Prevention of recurrent menstrual psychosis by an oral contraceptive. Am J Psychiatry. 1980;137(2):245–6.
71. Tunde-Ayinmode M, Singh AK, Marsden K. Improved functioning in a women with schizophrenia on exclusive therapy with oestrogen pills. Australas Psychiatry. 2008;10(4):403–4.
72. Lindamer LA, Lohr JB, Harris MJ, Jeste DV. Gender, estrogen, and schizophrenia. Psychopharmacol Bull. 1997;33(2):221–8.
73. Nordstrom AL, Olsson H, Halldin C. A pet study of d2 dopamine receptor density at different phases of the menstrual cycle. Psychiatry Res. 1998;83(1):1–6.
74. Di Paolo T. Modulation of brain dopamine transmission by sex steroids. Rev Neurosci. 1994;5(1):27–41.
75. Nordstrom AL, Farde L. Plasma prolactin and central d2 receptor occupancy in antipsychotic drug-treated patients. J Clin Psychopharmacol. 1998;18(4):305–10.
76. Crawford AM, Beasley Jr CM, Tollefson GD. The acute and long-term effect of olanzapine compared with placebo and haloperidol on serum prolactin concentrations. Schizophr Res. 1997;26(1):41–54.
77. Hamner MB, Arvanitis LA, Miller BG, Link CG, Hong WW. Plasma prolactin in schizophrenia subjects treated with seroquel (ici 204,636). Psychopharmacol Bull. 1996;32(1):107–10.
78. Bergemann N, Mundt C, Parzer P, Jannakos I, Nagl I, Salbach B, et al. Plasma concentrations of estradiol in women suffering from schizophrenia treated with conventional versus atypical antipsychotics. Schizophr Res. 2005;73(2–3):357–66.
79. Maric N, Popovic V, Jasovic-Gasic M, Pilipovic N, van Os J. Cumulative exposure to estrogen and psychosis: a peak bone mass, case-control study in first-episode psychosis. Schizophr Res. 2005;73(2–3):351–5.
80. Perlman WR, Webster MJ, Kleinman JE, Weickert CS. Reduced glucocorticoid and estrogen receptor alpha messenger ribonucleic acid levels in the amygdala of patients with major mental illness. Biol Psychiatry. 2004;56(11):844–52.
81. Perlman WR, Matsumoto M, Beltaifa S, Hyde TM, Saunders RC, Webster MJ, et al. Expression of estrogen receptor alpha exon-deleted mrna variants in the human and non-human primate frontal cortex. Neuroscience. 2005;134(1):81–95.
82. Perlman WR, Tomaskovic-Crook E, Montague DM, Webster MJ, Rubinow DR, Kleinman JE, et al. Alteration in estrogen receptor alpha mrna levels in frontal cortex and hippocampus of patients with major mental illness. Biol Psychiatry. 2005;58 (10):812–24.
83. Weickert CS, Miranda-Angulo AL, Wong J, Perlman WR, Ward SE, Radhakrishna V, et al. Variants in the estrogen receptor alpha gene and its mrna contribute to risk for schizophrenia. Hum Mol Genet. 2008;17(15):2293–309.
84. 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(3):247–52.
85. Kulkarni J, Riedel A, de Castella AR, Fitzgerald PB, Rolfe TJ, Taffe J, et al. Estrogen - a potential treatment for schizophrenia. Schizophr Res. 2001;48(1):137–44.
86. Kulkarni J, Riedel A, de Castella AR, Fitzgerald PB, Rolfe TJ, Taffe J, et al. A clinical trial of adjunctive oestrogen treatment in women with schizophrenia. Arch Wom Ment Health. 2002;5 (3):99–104.
87. Kulkarni J, de Castella A, Fitzgerald PB, Gurvich CT, Bailey M, Bartholomeusz C, et al. Estrogen in severe mental illness: a potential new treatment approach. Arch Gen Psychiatry. 2008;65 (8):955–60.
88. Akhondzadeh S, Nejatisafa AA, Amini H, Mohammadi MR, Larijani B, Kashani L, et al. Adjunctive estrogen treatment in women with chronic schizophrenia: a double-blind, randomized, and placebo-controlled trial. Progr Neuro Psychopharmacol Biol Psychiatr. 2003;27(6):1007–12.
89. Louza MR, Marques AP, Elkis H, Bassitt D, Diegoli M, Gattaz WF. Conjugated estrogens as adjuvant therapy in the treatment of acute schizophrenia: a double-blind study. Schizophr Res. 2004;66(2–3):97–100.
90. Bergemann N, Mundt C, Parzer P, Pakrasi M, Eckstein-Mannsperger U, Haisch S, et al. Estrogen as an adjuvant therapy to antipsychotics does not prevent relapse in women suffering from schizophrenia: results of a placebo-controlled double-blind study. Schizophr Res. 2005;74(2–3):125–34.
91. Bergemann N, Parzer P, Jaggy S, Auler B, Mundt C, Maier-Braunleder S. Estrogen and comprehension of metaphoric speech in women suffering from schizophrenia: results of a double-blind, placebo-controlled trial. Schizophr Bull. 2008;34(6):1172–81.
92. Lindamer LA, Buse DC, Lohr JB, Jeste DV. Hormone replacement therapy in postmenopausal women with schizophrenia: positive effect on negative symptoms? Biol Psychiatry. 2001;49(1):47–51.

93. Kulkarni J, Gurvich C, Lee SJ, Gilbert H, Gavrilidis E, de Castella A, et al. Piloting the effective therapeutic dose of adjunctive selective estrogen receptor modulator treatment in postmenopausal women with schizophrenia. Psychoneuroendocrinology. 2010;35(8):1142–7.
94. Kulkarni J, de Castella A, Headey B, Marston N, Sinclair K, Lee S, et al. Estrogens and men with schizophrenia: is there a case for adjunctive therapy? Schizophr Res. 2011;125(2–3):278–83.
95. Talih F, Fattal O, Malone Jr D. Anabolic steroid abuse: psychiatric and physical costs. Cleve Clin J Med. 2007;74 (5):341–4. 6, 9–52.
96. Rinieris P, Hatzimanolis J, Markianos M, Stefanis C. Effects of 4 weeks treatment with chlorpromazine and/or trihexyphenidyl on the pituitary-gonadal axis in male paranoid schizophrenics. Eur Arch Psychiatry Neurol Sci. 1988;237(4):189–93.
97. Rinieris P, Hatzimanolis J, Markianos M, Stefanis C. Effects of treatment with various doses of haloperidol on the pituitary-gonadal axis in male schizophrenic patients. Neuropsychobiology. 1989;22(3):146–9.
98. Kaneda Y, Fujii A. Effects of chronic neuroleptic administration on the hypothalamo-pituitary-gonadal axis of male schizophrenics. Progr Neuro Psychopharmacol Biol Psychiatr. 2000;24(2):251–8.
99. Brambilla F, Guerrini A, Riggi F, Ricciardi F. Psychoendocrine investigation in schizophrenia: relationship between pituitary-gonadal function and behavior. Dis Nerv Syst. 1974;35(8):362–7.
100. Brambilla F, Guerrini A, Guastalla A, Rovere C, Riggi F. Neuroendocrine effects of haloperidol therapy in chronic schizophrenia. Psychopharmacologia. 1975;44(1):17–22.
101. Brooksbank BW, MacSweeney DA, Johnson AL, Cunningham AE, Wilson DA, Coppen A. Androgen excretion and physique in schizophrenia. Br J Psychiatry. 1970;117(539):413–20.
102. Tourney G, Erb JL. Temporal variations in androgens and stress hormones in control and schizophrenic subjects. Biol Psychiatry. 1979;14(2):395–404.
103. Tourney G, Hatfield L. Plasma androgens in male schizophrenics. Arch Gen Psychiatry. 1972;27(6):753–5.
104. Ferrier IN, Cotes PM, Crow TJ, Johnstone EC. Gonadotropin secretion abnormalities in chronic schizophrenia. Psychol Med. 1982;12(2):263–73.
105. Cantalamessa L, Catania A, Silva A, Orsatti A, Baldini M, Mosca G, et al. Gonadotropin response to gonadotropin releasing hormone in acute schizophrenia. Progr Neuro Psychopharmacol Biol Psychiatr. 1984;8(3):411–7.
106. Oades RD, Schepker R. Serum gonadal steroid hormones in young schizophrenic patients. Psychoneuroendocrinology. 1994;19(4):373–85.
107. Brown AS, Hembree WC, Friedman JH, Kaufmann CA, Gorman JM. The gonadal axis in men with schizophrenia. Psychiatry Res. 1995;57(3):231–9.
108. Ritsner M, Gibel A, Ram E, Maayan R, Weizman A. Alterations in dhea metabolism in schizophrenia: two-month case-control study. Eur Neuropsychopharmacol. 2006;16(2):137–46.
109. Harris DS, Wolkowitz OM, Reus VI. Movement disorder, memory, psychiatric symptoms and serum dhea levels in schizophrenic and schizoaffective patients. World J Biol Psychiatry. 2001;2(2):99–102.
110. Brophy MH, Rush AJ, Crowley G. Cortisol, estradiol, and androgens in acutely ill paranoid schizophrenics. Biol Psychiatry. 1983;18(5):583–90.
111. Ceskova E, Prikryl R, Kasparek T. Testosterone in first-episode schizophrenia. Neuro Endocrinol Lett. 2007;28(6):811–4.
112. Huber TJ, Tettenborn C, Leifke E, Emrich HM. Sex hormones in psychotic men. Psychoneuroendocrinology. 2005;30 (1):111–4.
113. Taherianfard M, Shariaty M. Evaluation of serum steroid hormones in schizophrenic patients. Indian J Med Sci. 2004;58 (1):3–9.
114. van Rijn S, Aleman A, de Sonneville L, Sprong M, Ziermans T, Schothorst P, et al. Neuroendocrine markers of high risk for psychosis: Salivary testosterone in adolescent boys with prodromal symptoms. Psychol Med. 2011;41(3):499–508.
115. Shirayama Y, Hashimoto K, Suzuki Y, Higuchi T. Correlation of plasma neurosteroid levels to the severity of negative symptoms in male patients with schizophrenia. Schizophr Res. 2002;58 (1):69–74.
116. Goyal RO, Sagar R, Ammini AC, Khurana ML, Alias AG. Negative correlation between negative symptoms of schizophrenia and testosterone levels. Ann NY Acad Sci. 2004;1032:291–4.
117. Akhondzadeh S, Rezaei F, Larijani B, Nejatisafa AA, Kashani L, Abbasi SH. Correlation between testosterone, gonadotropins and prolactin and severity of negative symptoms in male patients with chronic schizophrenia. Schizophr Res. 2006;84(2–3):405–10.
118. Ko YH, Jung SW, Joe SH, Lee CH, Jung HG, Jung IK, et al. Association between serum testosterone levels and the severity of negative symptoms in male patients with chronic schizophrenia. Psychoneuroendocrinology. 2007;32(4):385–91.
119. Zumoff B, Strain GW, Miller LK, Rosner W, Senie R, Seres DS, et al. Plasma free and non-sex-hormone-binding-globulin-bound testosterone are decreased in obese men in proportion to their degree of obesity. J Clin Endocrinol Metab. 1990;71(4):929–31.
120. Ko YH, Lew YM, Jung SW, Joe SH, Lee CH, Jung HG, et al. Short-term testosterone augmentation in male schizophrenics: a randomized, double-blind, placebo-controlled trial. J Clin Psychopharmacol. 2008;28(4):375–83.
121. Strous RD, Maayan R, Lapidus R, Stryjer R, Lustig M, Kotler M, et al. Dehydroepiandrosterone augmentation in the management of negative, depressive, and anxiety symptoms in schizophrenia. Arch Gen Psychiatry. 2003;60(2):133–41.
122. Strous RD. Dehydroepiandrosterone (dhea) augmentation in the management of schizophrenia symptomatology. Essent Psychopharmacol. 2005;6(3):141–7.
123. Baulieu EE, Robel P. Dehydroepiandrosterone and dehydroepiandrosterone sulfate as neuroactive neurosteroids. J Endocrinol. 1996;150(Suppl):S221–39.
124. Ritsner MS, Gibel A, Ratner Y, Tsinovoy G, Strous RD. Improvement of sustained attention and visual and movement skills, but not clinical symptoms, after dehydroepiandrosterone augmentation in schizophrenia: a randomized, double-blind, placebo-controlled, crossover trial. J Clin Psychopharmacol. 2006;26(5):495–9.
125. Nachshoni T, Ebert T, Abramovitch Y, Assael-Amir M, Kotler M, Maayan R, et al. Improvement of extrapyramidal symptoms following dehydroepiandrosterone (dhea) administration in antipsychotic treated schizophrenia patients: a randomized, double-blind placebo controlled trial. Schizophr Res. 2005;79(2–3):251–6.
126. Honekopp J, Bartholdt L, Beier L, Liebert A. Second to fourth digit length ratio (2d:4d) and adult sex hormone levels: new data and a meta-analytic review. Psychoneuroendocrinology. 2007;32 (4):313–21.
127. Collinson SL, Lim M, Chaw JH, Verma S, Sim K, Rapisarda A, et al. Increased ratio of 2nd to 4th digit (2d:4d) in schizophrenia. Psychiatr Res. 176(1):8–12.
128. Koenig JI, Kirkpatrick B, Lee P. Glucocorticoid hormones and early brain development in schizophrenia. Neuropsychopharmacology. 2002;27(2):309–18.
129. van Os J, Selten JP. Prenatal exposure to maternal stress and subsequent schizophrenia. The may 1940 invasion of the Netherlands. Br J Psychiatry. 1998;172:324–6.

130. Zarrow MX, Philpott JE, Denenberg VH. Passage of 14c-4-corticosterone from the rat mother to the foetus and neonate. Nature. 1970;226(5250):1058–9.
131. Clancy B, Darlington RB, Finlay BL. Translating developmental time across mammalian species. Neuroscience. 2001;105 (1):7–17.
132. Kinnunen AK, Koenig JI, Bilbe G. Repeated variable prenatal stress alters pre- and postsynaptic gene expression in the rat frontal pole. J Neurochem. 2003;86(3):736–48.
133. Koenig JI, Elmer GI, Shepard PD, Lee PR, Mayo C, Joy B, et al. Prenatal exposure to a repeated variable stress paradigm elicits behavioral and neuroendocrinological changes in the adult offspring: potential relevance to schizophrenia. Behav Brain Res. 2005;156(2):251–61.
134. Lee PR, Brady DL, Shapiro RA, Dorsa DM, Koenig JI. Prenatal stress generates deficits in rat social behavior: reversal by oxytocin. Brain Res. 2007;1156:152–67.
135. Markham JA, Koenig JI. Prefrontal neuronal architecture is disrupted in the rat prenatal stress model of schizophrenia. Schizophr Bull. 2009;35(Supplement 1):137.
136. Markham JA, Koenig JI. Prenatal stress: role in psychotic and depressive diseases. Psychopharmacology. in press.
137. Markham JA, Taylor AR, Taylor SB, Bell DB, Koenig JI. Characterization of the cognitive impairments induced by prenatal exposure to stress in the rat. Front Behav Neurosci. 2010;4:Article 173.
138. Guillin O, Abi-Dargham A, Laruelle M. Neurobiology of dopamine in schizophrenia. Int Rev Neurobiol. 2007;78:1–39.
139. Creese I, Iversen SD. The pharmacological and anatomical substrates of the amphetamine response in the rat. Brain Res. 1975;83(3):419–36.
140. Markham JA, Mullins SE, Koenig JI. Peri-adolescent maturation of object recognition memory and associative memory is disrupted in male, but not female, rats exposed to prenatal stress. Society for Neuroscience Abstracts 2009:341.26.
141. Markham JA, Taylor AR, Shelton S, Brady-Bell D, Koenig JI. The repeated variable prenatal stress paradigm as a rodent model for schizophrenia. Neurobiology of Stress Workshop Abstracts; San Rafael, CA2008.
142. Steckler T, Drinkenburg WH, Sahgal A, Aggleton JP. Recognition memory in rats–ii. Neuroanatomical substrates. Prog Neurobiol. 1998;54(3):313–32.
143. Quirk GJ, Russo GK, Barron JL, Lebron K. The role of ventromedial prefrontal cortex in the recovery of extinguished fear. J Neurosci. 2000;20(16):6225–31.
144. Markham JA, Morris JR, Juraska JM. Neuron number decreases in the rat ventral, but not dorsal, medial prefrontal cortex between adolescence and adulthood. Neuroscience. 2007;144 (3):961–8.
145. Sowell ER, Thompson PM, Holmes CJ, Jernigan TL, Toga AW. *In vivo* evidence for post-adolescent brain maturation in frontal and striatal regions. Nat Neurosci. 1999;2(10):859–61.
146. Giedd JN, Blumenthal J, Jeffries NO, Castellanos FX, Liu H, Zijdenbos A, et al. Brain development during childhood and adolescence: a longitudinal mri study. Nat Neurosci. 1999;2 (10):861–3.
147. Brown AS, Susser ES. In utero infection and adult schizophrenia. Ment Retard Dev Disabil Res Rev. 2002;8(1):51–7.
148. Meyer U, Feldon J, Fatemi SH. *In-vivo* rodent models for the experimental investigation of prenatal immune activation effects in neurodevelopmental brain disorders. Neurosci Biobehav Rev. 2009;33(7):1061–79.
149. Markham JA. Sex steroids and schizophrenia. Reviews in Endocrine and Metabolic Disorders. accepted in revision.
150. Fortier ME, Luheshi GN, Boksa P. Effects of prenatal infection on prepulse inhibition in the rat depend on the nature of the infectious agent and the stage of pregnancy. Behav Brain Res. 2007;181(2):270–7.
151. Romero E, Ali C, Molina-Holgado E, Castellano B, Guaza C, Borrell J. Neurobehavioral and immunological consequences of prenatal immune activation in rats. Influence of antipsychotics. Neuropsychopharmacology. 2007;32(8):1791–804.
152. Borrell J, Vela JM, Arevalo-Martin A, Molina-Holgado E, Guaza C. Prenatal immune challenge disrupts sensorimotor gating in adult rats. Implications for the etiopathogenesis of schizophrenia. Neuropsychopharmacology. 2002;26(2):204–15.
153. Swerdlow NR, Weber M, Qu Y, Light GA, Braff DL. Realistic expectations of prepulse inhibition in translational models for schizophrenia research. Psychopharmacology. 2008;199(3):331–88.
154. Powell SB, Zhou X, Geyer MA. Prepulse inhibition and genetic mouse models of schizophrenia. Behav Brain Res. 2009;204 (2):282–94.
155. Braff DL, Geyer MA, Swerdlow NR. Human studies of prepulse inhibition of startle: normal subjects, patient groups, and pharmacological studies. Psychopharmacology. 2001;156(2–3):234–58.
156. Romero E, Guaza C, Castellano B, Borrell J. Ontogeny of sensorimotor gating and immune impairment induced by prenatal immune challenge in rats: Implications for the etiopathology of schizophrenia. Mol Psychiatr. 2008.
157. Kumari V, Aasen I, Sharma T. Sex differences in prepulse inhibition deficits in chronic schizophrenia. Schizophr Res. 2004;69(2–3):219–35.
158. Meyer U, Feldon J, Schedlowski M, Yee BK. Towards an immuno-precipitated neurodevelopmental animal model of schizophrenia. Neurosci Biobehav Rev. 2005;29(6):913–47.
159. Meyer U, Nyffeler M, Schwendener S, Knuesel I, Yee BK, Feldon J. Relative prenatal and postnatal maternal contributions to schizophrenia-related neurochemical dysfunction after in utero immune challenge. Neuropsychopharmacology. 2008;33 (2):441–56.
160. Schwendener S, Meyer U, Feldon J. Deficient maternal care resulting from immunological stress during pregnancy is associated with a sex-dependent enhancement of conditioned fear in the offspring. J Neurodevelop Disord. 2009;1:15–32.
161. Morris JA, Jordan CL, Breedlove SM. Sexual differentiation of the vertebrate nervous system. Nat Neurosci. 2004;7 (10):1034–9.
162. Schulz KM, Molenda-Figueira HA, Sisk CL. Back to the future: the organizational-activational hypothesis adapted to puberty and adolescence. Horm Behav. 2009;55(5):597–604.
163. Lewis DA, Sweet RA. Schizophrenia from a neural circuitry perspective: advancing toward rational pharmacological therapies. J Clin Investig. 2009;119(4):706–16.
164. Stander N, Wagner WM, Goddard A, Kirberger RM. Ultrasonographic appearance of canine parvoviral enteritis in puppies. Vet Radiol Ultrasound. 51(1):69–74.
165. Lenroot RK, Gogtay N, Greenstein DK, Wells EM, Wallace GL, Clasen LS, et al. Sexual dimorphism of brain developmental trajectories during childhood and adolescence. Neuroimage. 2007;36(4):1065–73.
166. Shaw P, Greenstein D, Lerch J, Clasen L, Lenroot R, Gogtay N, et al. Intellectual ability and cortical development in children and adolescents. Nature. 2006;440(7084):676–9.
167. Sowell ER, Thompson PM, Leonard CM, Welcome SE, Kan E, Toga AW. Longitudinal mapping of cortical thickness and brain growth in normal children. J Neurosci. 2004;24(38):8223–31.
168. Giedd JN, Castellanos FX, Rajapakse JC, Vaituzis AC, Rapoport JL. Sexual dimorphism of the developing human brain. Progr Neuro Psychopharmacol Biol Psychiatr. 1997;21(8):1185–201.
169. Raznahan A, Lee Y, Stidd R, Long R, Greenstein D, Clasen L, et al. Longitudinally mapping the influence of sex and androgen

signaling on the dynamics of human cortical maturation in adolescence. Proc Natl Acad Sci USA. 2010;107(39):16988–93.
170. Reid SN, Juraska JM. Sex differences in the gross size of the rat neocortex. J Comp Neurol. 1992;321(3):442–7.
171. Nunez JL, Sodhi J, Juraska JM. Ovarian hormones after postnatal day 20 reduce neuron number in the rat primary visual cortex. J Neurobiol. 2002;52(4):312–21.
172. Kim JH, Juraska JM. Sex differences in the development of axon number in the splenium of the rat corpus callosum from postnatal day 15 through 60. Brain Res. 1997;102(1):77–85.
173. Yates MA, Juraska JM. Pubertal ovarian hormone exposure reduces the number of myelinated axons in the splenium of the rat corpus callosum. Exp Neurol. 2008;209(1):284–7.
174. Rubinow MJ, Juraska JM. Neuron and glia numbers in the basolateral nucleus of the amygdala from preweaning through old age in male and female rats: a stereological study. J Comp Neurol. 2009;512(6):717–25.
175. Koss WA, Belden CE, Decker SK, Juraska JM. Dendritic remodeling over the adolescent period in the basolateral amygdala of male and female rats. Society for Neuroscience Abstracts. 2009:508.8.
176. Zehr JL, Todd BJ, Schulz KM, McCarthy MM, Sisk CL. Dendritic pruning of the medial amygdala during pubertal development of the male syrian hamster. J Neurobiol. 2006;66(6):578–90.
177. Ahmed EI, Zehr JL, Schulz KM, Lorenz BH, DonCarlos LL, Sisk CL. Pubertal hormones modulate the addition of new cells to sexually dimorphic brain regions. Nat Neurosci. 2008;11 (9):995–7.
178. Meyer G, Ferres-Torres R, Mas M. The effects of puberty and castration on hippocampal dendritic spines of mice. A golgi study. Brain Res. 1978;155(1):108–12.
179. Teicher MH, Andersen SL, Hostetter Jr JC. Evidence for dopamine receptor pruning between adolescence and adulthood in striatum but not nucleus accumbens. Brain Res. 1995;89 (2):167–72.
180. Andersen SL, Thompson AT, Rutstein M, Hostetter JC, Teicher MH. Dopamine receptor pruning in prefrontal cortex during the periadolescent period in rats. Synapse NY NY. 2000;37(2):167–9.
181. Andersen SL, Rutstein M, Benzo JM, Hostetter JC, Teicher MH. Sex differences in dopamine receptor overproduction and elimination. Neuroreport. 1997;8(6):1495–8.
182. Andersen SL, Thompson AP, Krenzel E, Teicher MH. Pubertal changes in gonadal hormones do not underlie adolescent dopamine receptor overproduction. Psychoneuroendocrinology. 2002;27(6):683–91.
183. Kalsbeek A, Voorn P, Buijs RM, Pool CW, Uylings HB. Development of the dopaminergic innervation in the prefrontal cortex of the rat. J Comp Neurol. 1988;269(1):58–72.
184. Benes FM, Vincent SL, Molloy R, Khan Y. Increased interaction of dopamine-immunoreactive varicosities with gaba neurons of rat medial prefrontal cortex occurs during the postweanling period. Synapse NY NY. 1996;23(4):237–45.
185. Tseng KY, O'Donnell P. D2 dopamine receptors recruit a gaba component for their attenuation of excitatory synaptic transmission in the adult rat prefrontal cortex. Synapse NY NY. 2007;61 (10):843–50.
186. Tseng KY, O'Donnell P. Dopamine modulation of prefrontal cortical interneurons changes during adolescence. Cereb Cortex. 2007;17(5):1235–40.
187. Heng L, Markham JA, Hu XT, Tseng KY. Concurrent upregulation of postsynaptic l-type ca(2+) channel function and protein kinase a signaling is required for the periadolescent facilitation of ca(2+) plateau potentials and dopamine d1 receptor modulation in the prefrontal cortex. Neuropharmacology. in press.
188. Cunningham MG, Bhattacharyya S, Benes FM. Amygdalocortical sprouting continues into early adulthood: Implications for the development of normal and abnormal function during adolescence. J Comp Neurol. 2002;453(2):116–30.
189. Cressman VL, Balaban J, Steinfeld S, Shemyakin A, Graham P, Parisot N, et al. Prefrontal cortical inputs to the basal amygdala undergo pruning during late adolescence in the rat. J Comp Neurol. 2010;518(14):2693–709.
190. Becker JB. Gender differences in dopaminergic function in striatum and nucleus accumbens. Pharmacol Biochem Behav. 1999;64(4):803–12.
191. Shrenker P, Maxson SC, Ginsburg BE. The role of postnatal testosterone in the development of sexually dimorphic behaviors in dba/1bg mice. Physiol Behav. 1985;35(5):757–62.
192. Eichmann F, Holst DV. Organization of territorial marking behavior by testosterone during puberty in male tree shrews. Physiol Behav. 1999;65(4–5):785–91.
193. Pellis SM. Sex differences in play fighting revisited: traditional and nontraditional mechanisms of sexual differentiation in rats. Arch Sex Behav. 2002;31(1):17–26.
194. Schulz KM, Zehr JL, Salas-Ramirez KY, Sisk CL. Testosterone programs adult social behavior before and during, but not after, adolescence. Endocrinology. 2009;150(8):3690–8.
195. Brand T, Slob AK. Peripubertal castration of male rats, adult open field ambulation and partner preference behavior. Behav Brain Res. 1988;30(2):111–7.
196. Primus RJ, Kellogg CK. Gonadal hormones during puberty organize environment-related social interaction in the male rat. Horm Behav. 1990;24(3):311–23.
197. Levin HS, Culhane KA, Hartmann J, Evankovich K, Mattson AJ, Harward H, et al. Developmental changes in performance on tests of purported frontal lobe functioning. Dev Neuropsych. 1991;7(3):377–95.
198. Kanit L, Taskiran D, Yilmaz OA, Balkan B, Demirgoren S, Furedy JJ, et al. Sexually dimorphic cognitive style in rats emerges after puberty. Brain Res Bull. 2000;52(4):243–8.
199. Hier DB, Crowley Jr WF. Spatial ability in androgen-deficient men. N Engl J Med. 1982;306(20):1202–5.
200. Markham JA. Peri-adolescent gonadal steroids organize adult sex differences in prefrontal-dependent extinction of a conditioned fear memory. In preparation.
201. Morgan MA, LeDoux JE. Differential contribution of dorsal and ventral medial prefrontal cortex to the acquisition and extinction of conditioned fear in rats. Behav Neurosci. 1995;109(4):681–8.
202. Van den Buuse M, Eikelis N. Estrogen increases prepulse inhibition of acoustic startle in rats. Eur J Pharmacol. 2001;425 (1):33–41.
203. Gogos A, Nathan PJ, Guille V, Croft RJ, van den Buuse M. Estrogen prevents 5-ht1a receptor-induced disruptions of prepulse inhibition in healthy women. Neuropsychopharmacology. 2006;31(4):885–9.
204. Weiner I. The "Two-headed" Latent inhibition model of schizophrenia: modeling positive and negative symptoms and their treatment. Psychopharmacology. 2003;169(3–4):257–97.
205. Nofrey BS, Ben-Shahar OM, Brake WG. Estrogen abolishes latent inhibition in ovariectomized female rats. Brain Cogn. 2008;66(2):156–60.
206. Arad M, Weiner I. Disruption of latent inhibition induced by ovariectomy can be reversed by estradiol and clozapine as well as by co-administration of haloperidol with estradiol but not by haloperidol alone. Psychopharmacology. 2009;206(4):731–40.
207. Arad M, Weiner I. Sex-dependent antipsychotic capacity of 17beta-estradiol in the latent inhibition model: a typical antipsychotic drug in both sexes, atypical antipsychotic drug in males. Neuropsychopharmacology. 2010;35(11):2179–92.
208. Koller WC, Weiner WJ, Klawans HL, Nausieda PA. Influence of female sex hormones on neuroleptic-induced behavioral supersensitivity. Neuropharmacology. 1980;19(4):387–91.

209. Foreman MM, Porter JC. Effects of catechol estrogens and catecholamines on hypothalamic and corpus striatal tyrosine hydroxylase activity. J Neurochem. 1980;34(5):1175–83.
210. Bedard P, Boucher R, Di Paolo T, Labrie F. Interaction between estradiol, prolactin, and striatal dopaminergic mechanisms. Adv Neurol. 1984;40:489–95.
211. Bedard PJ, Boucher R, Daigle M, Di Paolo T. Similar effect of estradiol and haloperidol on experimental tardive dyskinesia in monkeys. Psychoneuroendocrinology. 1984;9(4):375–9.
212. Hafner 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(2):125–34.
213. Swerdlow NR, Auerbach P, Monroe SM, Hartston H, Geyer MA, Braff DL. Men are more inhibited than women by weak prepulses. Biol Psychiatry. 1993;34(4):253–60.
214. Swerdlow NR, Hartman PL, Auerbach PP. Changes in sensorimotor inhibition across the menstrual cycle: implications for neuropsychiatric disorders. Biol Psychiatry. 1997;41 (4):452–60.
215. Koch M. Sensorimotor gating changes across the estrous cycle in female rats. Physiol Behav. 1998;64(5):625–8.
216. Becker JB. Direct effect of 17 beta-estradiol on striatum: sex differences in dopamine release. Synapse NY NY. 1990;5 (2):157–64.
217. Markham JA, Juraska JM. Social recognition memory: influence of age, sex, and ovarian hormonal status. Physiol Behav. 2007;92 (5):881–8.
218. Thor DH. Testosterone and persistance of social investigation in laboratory rats. J Comp Physiol Psychol. 1980;94(5):970–6.
219. Thor DH, Wainwright KL, Holloway WR. Persistence of attention to a novel conspecific: some developmental variables in laboratory rats. Dev Psychobiol. 1982;15(1):1–8.
220. Dohanich GP. Gonadal steroids, learning and memoroy. In: Pfaff DW, Arnold AP, Etgen SE, Fahrbach SE, Rubin RT, editors. Hormones, brain and behavior. San Diego: Academic Press (Elsevier Science); 2002. p. 265–327.
221. Jonasson Z. Meta-analysis of sex differences in rodent models of learning and memory: a review of behavioral and biological data. Neurosci Biobehav Rev. 2005;28(8):811–25.