CNS Drugs (2016) 30:125–133
DOI 10.1007/s40263-016-0312-0

LEADING ARTICLE

Potential Role of Oestrogen Modulation in the Treatment of Neurocognitive Deficits in Schizophrenia

Thomas W. Weickert[1,2,3] · Katherine M. Allen[1,2,3] · Cynthia S. Weickert[1,2,3]

Published online: 5 February 2016

Abstract Cognitive deficits are prevalent in schizophrenia, and these deficits represent a disabling aspect of the illness for which there are no current effective treatments. Recent work has shown that sex hormone levels correlate with brain activity and cognitive abilities differentially in patients with schizophrenia relative to healthy control groups. There is emerging evidence suggesting that oestrogen-based therapies may be useful in reversing the cognitive deficits associated with schizophrenia. To date, the results from clinical trials using oestrogen-based therapies to reverse cognitive impairment in schizophrenia have shown that the selective oestrogen receptor modulator raloxifene may be useful to improve attention, memory, learning and the associated brain activity in chronically ill men and women with schizophrenia or schizoaffective disorder. While these findings of cognitive enhancement with a selective oestrogen receptor modulator in people with schizophrenia are encouraging, additional studies will be required to replicate the initial results, assess the time frame of treatment effects, identify biomarkers in subsets of patients who may be more likely to optimally respond to treatment, and identify a more precise mechanism of action, which may include anti-inflammatory effects of oestrogen-based treatments.

✉ Thomas W. Weickert
t.weickert@unsw.edu.au

[1] School of Psychiatry, University of New South Wales, Sydney, NSW, Australia

[2] Neuroscience Research Australia, Barker Street, Randwick, Sydney, NSW 2031, Australia

[3] Schizophrenia Research Institute, Sydney, NSW, Australia

Key Points

Cognitive deficits are a disabling aspect of schizophrenia, for which there are no treatments.

Oestrogen-based therapies for cognitive remediation have support from animal and human studies.

The selective oestrogen receptor modulator raloxifene has been shown to improve attention and memory in men and women with schizophrenia.

1 Neurocognitive Deficits in Patients with Schizophrenia, and Their Impact

Schizophrenia is a debilitating mental disorder, characterized by psychotic symptoms—which can be reduced in severity via current antipsychotic treatments—and by negative symptoms (such as inappropriate emotional responses and lack of socialization) and cognitive deficits, both of which are generally unresponsive to current treatments. Cognitive deficits in schizophrenia are heterogeneous to the extent that most people with schizophrenia display impairment across a wide range of cognitive domains, whereas others may appear to display little to no cognitive impairment, relative to healthy comparison groups. The cognitive deficits associated with schizophrenia are disabling, such that these deficits are related to functional impairment, which limits the ability of these patients to attain educational goals and hold meaningful employment [1].

In a relatively large sample of chronically ill patients, we showed that people with schizophrenia could be classified into three distinct groups on the basis of their degree

of intellectual decline from a premorbid IQ estimate, and these three groups displayed distinct patterns of cognitive abilities versus deficits [2]. Approximately half of the patients displayed a large (>10-point) reduction in their current IQ estimates in relation to their premorbid IQ estimates. These patients displayed impairment in the cognitive domains of executive function and attention (i.e. prefrontal cortex function) and memory (i.e. hippocampal function); this group was referred to as the 'deteriorated' group. The other half of the patients did not display a large decline in their intellectual abilities; however, approximately half of this half of patients (i.e. 25 % of the total sample) displayed little to no change from low premorbid IQ estimates (this group was referred to as the 'compromised' group), while the other half (i.e. 25 % of the total sample) appeared to display little to no change from high premorbid IQ estimates (this group was referred to as the 'preserved' group). The compromised group displayed the most widespread impairment across all cognitive domains we assessed (including executive function, attention, memory, language and visuospatial perceptual abilities). Conversely, the preserved group displayed impairment restricted to the cognitive domains of executive function and attention when compared with an IQ-matched group of healthy controls. However, both deteriorated and preserved patients typically perform below their premorbid level of cognitive function or potential, e.g. relative to their identical twin who is discordant for the illness [2, 3]; thus, the optimal aim would be to restore cognitive abilities in these patients to their previous potential and, to the extent possible, improve the cognitive function of those patients in the compromised group. Since our original classification of people with schizophrenia on the basis of their intellectual decline from premorbid IQ estimates [2], the heterogeneity of the cognitive deficits and the reliability and validity of this classification mechanism of people with schizophrenia into IQ-based subgroups have been demonstrated through replication in both chronically ill [4–6] and first-episode patient samples [7–9]. In a larger, independent replication sample, we showed that all three of these IQ-based subgroups have room for cognitive improvement, with significant difficulties in engaging socially and in attaining life goals [5].

Human cognition includes a wide range of learning and memory abilities, with only a portion of these abilities being routinely assessed in studies of people with schizophrenia; however, most studies have included some measure of declarative memory. Declarative cognitive processes typically involve the hippocampal formation and are characterized by conscious awareness and effort [10]. Conversely, non-declarative cognitive processes are characterized by automatization with no conscious awareness of the process, and recruit cortical or subcortical brain regions other than the hippocampus [10]. Non-declarative cognitive processes are less commonly assessed in studies of people with schizophrenia. Standardized cognitive batteries that assess declarative cognitive processes typically show marked performance deficits of 1–1.5 standard deviations below the mean on average in people with schizophrenia [2]; while studies of non-declarative cognitive processes in people with schizophrenia initially showed no non-declarative deficit [11], others now more commonly report significant impairment in some non-declarative cognitive processes [12]. In one form of non-declarative cognitive processing called 'probabilistic association learning', people gradually learn the probability-based relationships between cues and outcomes. People with schizophrenia display a reduced learning rate and an overall performance deficit in probabilistic association learning, relative to healthy controls [12]. In relation to the neural substrate of probabilistic association learning, healthy adults typically show decreased hippocampal activity and increased striatal (caudate nucleus) activity [13, 14], whereas people with schizophrenia show reduced frontal–striatal activity in conjunction with an overall performance deficit [15]. However, a proportion of people with schizophrenia who are able to learn probabilistic associations show reduced striatal (caudate nucleus) activity and increased hippocampal formation activity [15]. Thus, some people with schizophrenia appear to learn the probabilistic relationship using a different neural network than that used by healthy controls, suggesting that there is capacity for some form of neural compensation that may be accessed to improve cognition in people with schizophrenia.

In general, cognitive deficits in schizophrenia have been associated with functional impairment, i.e. impairment of the ability to perform at work or school [1]. Nuechterlein and colleagues [16] showed that neurocognitive factors in the three broad domains of working memory, attention/perception, and verbal memory/processing speed predicted 52 % of the variance related to returning to school or work after 9 months in first-episode schizophrenia patients. Hoe and colleagues [17] showed that both neurocognition (general mental processing) and social cognition (mental processing that underlies social interactions) may be causally relevant to functional outcome in people with schizophrenia. Harvey and colleagues [18] showed that many people with schizophrenia display impairment across multiple functional domains, and they tend to remain functionally impaired throughout their life. Thus, identifying treatments—pharmacological or otherwise—that will restore cognitive function in people with schizophrenia should confer a substantial benefit on their functional abilities, in addition to their quality of life. However, although there have been numerous studies of

pharmacological agents aimed at improving cognition in schizophrenia, there has been a paucity of studies showing reversal of cognitive deficits with pharmacological treatments in people with schizophrenia.

To date, the findings from studies of pharmaceutical treatments for remediation of cognitive deficits in people with schizophrenia have been mixed, with some studies showing improvement with treatment and others generally showing no significant improvement, relative to placebo. Using an alpha-7 nicotinic receptor agonist, Keefe and colleagues [19] showed significant improvement in performance on the CogState battery [20] with relatively small effect sizes (Cohen's $d = 0.26$), but no significant improvement on the Measurement And Treatment Research to Improve Cognition in Schizophrenia (MATRICS) battery [21]. Although administration of a generalized attention-enhancing agent (modafinil) with an uncertain mechanism of action elicited enhanced cortical gamma-range oscillatory power [22], other studies [23] failed to find significant differences between modafinil treatment and placebo on assays of trained tasks and cognitive measures from the MATRICS battery. Given that cognitive deficits are related to functional impairment, which prevents full recovery, and that no effective pharmacological treatments for cognitive deficits are presently available, there remains an urgent need to identify novel pharmacological treatments to reverse cognitive deficits in people with schizophrenia.

2 Rationale for Investigating Oestrogenic Therapies to Treat Cognitive Deficits in Schizophrenia

There is recent evidence to suggest that cognitive deficits in people with schizophrenia may benefit from treatment with oestrogen-based therapies. On the basis of correlational studies, two independent studies [24, 25] showed significant positive relationships between circulating oestrogen levels and cognitive performance in women with schizophrenia. Using functional magnetic resonance imaging (fMRI), Mendrek and colleagues [26] showed a significant positive correlation between sex hormone levels and brain activity in healthy men and women with schizophrenia during a spatial rotation test, but there was no such relationship in healthy women and men with schizophrenia.

There is also a large and fairly well developed knowledge base demonstrating that oestrogen promotes neurotrophin synthesis, protects the brain against stress and inflammation, and has pro-cognitive effects. While the molecular substrates of cognitive deficits in schizophrenia are largely unknown, some evidence suggests that hormonal–inflammation interactions may have a modulatory role in cognitive protection–impairment. We reported an increased frequency of markers of inflammation (elevated cytokine expression) in the brains of people with schizophrenia relative to control groups from two independent cohorts [27, 28]. Furthermore, we also recently showed significant inverse relationships of peripheral cytokine levels to a specific neurocognitive ability (i.e. language as measured by verbal fluency) and the brain volume of Broca's area (which is a brain region related to speech production) in people with schizophrenia [29], suggesting a link between increased inflammation and poor cognition.

Animal studies have shown that increased cytokine levels may negatively impact cognition. In rodents, dam exposure to the cytokines interleukin-1β (IL-1β) and tumour necrosis factor alpha (TNF-α) reduced neuronal dendrites and dendritic length in pups [30]. Stress can increase levels of IL-1β in the hippocampus [31], and IL-1β can inhibit adult hippocampal neurogenesis, which can be reversed by blockade of IL-1β [32]. Peripheral and central IL-1β administration elicits anhedonia and deficits in social interaction and memory [32, 33], which are similar to behavioural deficits that occur in schizophrenia. Thus, treatments that are capable of reducing cytokine levels may also reverse cognitive impairment in schizophrenia. Interestingly, oestrogen has been shown to have anti-inflammatory effects by reducing cytokine levels [34–39].

Given the negative effects of cytokines on cognition, the reduced cytokine levels elicited by oestrogen [34–39] may concurrently improve cognition. However, treatments targeting inflammation in schizophrenia have also shown mixed results. In schizophrenia trials, the antibiotic minocycline improved executive (prefrontal cortex) function [40]; however, aspirin did not improve cognition [41]. Importantly, it should be noted that these studies did not stratify patients on the basis of increased/decreased cytokine levels prior to administration of the anti-inflammatory agents; thus, the effect of the anti-inflammatory agent in these studies may have been diluted by inclusion of patients both with and without inflammation.

Sex hormones in general, and oestrogen in particular, may have protective effects in relation to schizophrenia, given that a slightly smaller proportion of females develop schizophrenia, relative to males (2:3), and that in females who do develop schizophrenia, their symptom severity is greater when oestrogen levels are low, such as at times of the oestrous cycle when oestrogen is low, or after menopause [42]. Testosterone can also be converted to oestrogen in the brain by the aromatase enzyme; thus, oestrogen receptor binding and oestrogen action in the brain can also be relevant in men as well as in women.

In a series of studies, we showed differential relationships between cognitive function, brain activity and circulating testosterone levels in healthy men and men with schizophrenia. We showed that circulating testosterone levels explain 13–21 % of the unique variance in relation to verbal memory, working memory and processing speed in chronically ill men with schizophrenia, whereas no such relationship exists in healthy men [43]. Additionally, in men with schizophrenia, circulating testosterone levels were inversely related to prefrontal cortex activity during inhibition of emotional words [44] and positively related to inferior frontal cortex activity during recognition of angry faces [45], whereas no such relationship existed in healthy men in these studies. Conversely, while healthy men displayed a positive relationship between circulating testosterone levels and brain activity in the ventral striatum during positive prediction error (a measure of unexpected reward) and an inverse relationship between circulating testosterone levels and ventral striatum activity during negative prediction error (a measure of unexpected omission of reward), men with schizophrenia showed no such relationships between circulating testosterone levels and ventral striatal activity [46]. Circulating testosterone levels in men with schizophrenia in these studies did not differ significantly from those in healthy men. Thus, variation in normal testosterone levels may be capable of modulating cognitive abilities and related brain activity differently in men with schizophrenia versus healthy men, and these relationships appear to be dependent on task demands and the brain region (e.g. cortical versus subcortical) typically relevant to the task. Additionally, as noted above, these sex steroid relationships may be working through either the oestrogen receptor in the brains of women with schizophrenia or through both the androgen receptor and/or the oestrogen receptor in the brains of men with schizophrenia.

It is important to consider that not only could the circulating levels of sex hormones be altered in schizophrenia, for which the evidence is mixed [43, 47–50], but also it may be that the brain response to these hormones is attenuated. Indeed, from a molecular brain perspective, we found that men and women with schizophrenia displayed reduced messenger RNA (mRNA) levels of oestrogen receptor alpha (ESR-1) in the hippocampus [51] and decreased frequencies of wild-type ESR-1 mRNA in the prefrontal cortex [52], which would be indicative of an attenuated oestrogen response. Using an in vitro luciferase assay to monitor gene expression, we confirmed that the altered form of the oestrogen receptor, which is found more often in the brains of people with schizophrenia, works as a dominant negative, antagonising/blocking the activity of wild-type ER [52]. Thus, not only could low blood levels of oestrogen contribute to cognitive deficits, but also the presence of altered oestrogen receptors in the hippocampus and cortex could also likely contribute to the cognitive deficits that are observed [51, 52]. Therefore, stimulation of oestrogen receptors in the brains of men and women with schizophrenia may improve or restore cognitive ability.

There is already a precedent for treatment with additional oestrogen to benefit memory and attention in both animals and in humans. First, we will consider a few examples from work in animals. Following early studies suggesting that oestrogen can influence spine density in the hippocampus [53, 54], a number of studies focused on the influence of oestrogen in hippocampal-based spatial memory, and these studies found that oestrogen is generally beneficial to spatial working memory in young and aged female rats [55–58]. Oestrogen also enhances non-spatial memory, including associative memory [59], non-spatial working memory [60] and episodic memory, such as object placement and recognition [61]. However, other studies have suggested that oestrogen can impair performance in spatial memory tasks [62, 63]. Oestrogen administration can also enhance visuospatial attention in young ovariectomised and aged female rats [64] and monkeys [65], but may not influence reaction time in monkeys [65]. Therefore, oestrogen effects may depend on the dose, duration and timing of oestrogen administration, as well as on the context and specific cognitive domain used to perform the task.

In relation to humans, there is also mixed evidence in favour of oestrogen-based treatments for cognitive impairment in individuals of advanced age. While some studies of older, postmenopausal women demonstrated cognitive enhancement with oestrogen replacement therapy [66], other work failed to demonstrate restoration of cognitive deficits in postmenopausal women with dementia [67]. It is thought that the lack of a beneficial effect of oestrogen on aged brain function may have to do with the timing of oestrogen replacement (with longer delays after menopause being less effective) or the effects of comorbidity from hypertension and/or diabetes in older adults [68, 69]. In addition to the mixed results of oestrogen replacement therapy to reverse cognitive deficits in older women, oestrogen replacement therapy alone is associated with increased breast and uterine cancer in females and feminizing effects in males. Thus, other oestrogen-based treatments targeting the brain that would not have the general adverse events common to direct oestrogen therapy would be optimal.

The selective oestrogen receptor modulator (SERM) raloxifene has antagonist effects on the oestrogen receptor in the breast and uterus without feminizing effects in males [70], and has agonistic effects on the oestrogen receptor in bone and in brain tissue [71]. Preclinical studies provided evidence that raloxifene acts in an oestrogen-like manner in

the mammalian brain, e.g. raloxifene mimics the effects of oestrogen on various parameters of dopamine and serotonin neurotransmission [71–74]. Importantly, raloxifene has been shown to prevent age-related cognitive decline in brain activity during memory tests in healthy older men [75, 76]. In postmenopausal women, raloxifene treatment at 120 mg daily, but not at 60 mg daily, reduced the age-related decline in attention and verbal memory, and reduced the risk of developing mild cognitive impairment [77]. Thus, raloxifene is an oestrogen-based pharmacological agent with potential to reverse cognitive deficits in men and women with schizophrenia. However, the exact neurobiological mechanisms by which raloxifene acts in the human brain regions integral to cognition (including the hippocampus and cerebral cortex) have not been fully elucidated to date.

3 Clinical Findings from Studies of Oestrogen-Based Treatment Trials to Reverse Cognitive Deficits in Schizophrenia

There is mixed evidence regarding the effectiveness of using oestrogen-based treatments to reverse the cognitive deficits associated with schizophrenia (see Table 1). One study reported specific improvement in speech comprehension with administration of 17β-oestradiol in women with schizophrenia [78]. However, using a transdermal oestradiol patch therapy, Kulkarni and colleagues [79] failed to show improvement in cognitive abilities in women with schizophrenia as measured by the Repeatable Battery for the Assessment of Neuropsychological Status [80], although those women with schizophrenia did demonstrate significant reductions in psychotic symptoms, relative to use of placebo. Similarly, administration of dehydroepiandrosterone (DHEA), an intermediate in the synthesis of sex steroids, produced mixed results, with some studies showing improvement in attention and skill learning [81, 82], while others reported no significant benefits of DHEA treatment in schizophrenia [83, 84]. While the results of studies using oestrogen and DHEA to improve cognition in schizophrenia appear to be mixed, other studies using oestrogen-related therapies (specifically the SERM raloxifene), have provided more consistent results to date, although the number of studies using raloxifene to treat cognitive deficits in schizophrenia is small.

Oestrogen-based treatment (specifically the SERM raloxifene) has been shown to reduce positive symptoms (including thought derailment/disorder) and generalized anxiety [85, 86], all of which may be putatively elicited/exacerbated by trauma, prenatal infection and/or substance abuse/dependence. Huerta-Ramos and colleagues [87] showed significant improvements in executive function and memory with administration of 60 mg of raloxifene daily for 12 weeks in a small sample of between 16 and 26 postmenopausal women with schizophrenia. More recently, in a larger randomized, double-blind, placebo-controlled, cross-over study of 98 adult men and women with schizophrenia or schizoaffective disorder (mean age 35 years) we showed significant improvements (with medium to large effect sizes) in attention and memory with administration of 120 mg of raloxifene daily for 6 weeks [88]. Additionally, in a subset of patients from our raloxifene trial, who received fMRI, 19 men and women with schizophrenia or schizoaffective disorder displayed significant improvement in a better probabilistic association learning test (a test of non-declarative cognitive processes) in conjunction with increased hippocampal activity

Table 1 Summary of cognitive outcomes from oestrogen-based treatment trials in schizophrenia

Study, year	Treatment	Sample	Outcome
Bergemann et al. [78], 2008	Oestradiol	Women with schizophrenia	Significant speech comprehension improvement
Kulkarni et al. [79], 2015	Oestradiol	Women with schizophrenia	No significant cognitive improvement
Ritsner et al. [82], 2006	DHEA	Men and women with schizophrenia	Significant attention and skill learning improvement
Ritsner et al. [83], 2010	DHEA	Men and women with schizophrenia	DHEA negative predictor of cognition
Strous et al. [84], 2007	DHEA	Men and women with schizophrenia	No significant cognitive improvement
Huerta-Ramos et al. [87], 2014	Raloxifene	Women with schizophrenia	Significant executive function and memory improvement
Weickert et al. [88], 2015	Raloxifene	Men and women with schizophrenia	Significant memory and attention improvement
Kindler et al. [89], 2015	Raloxifene	Men and women with schizophrenia	Significant improvement in learning and increased brain activity

DHEA dehydroepiandrosterone

following administration of 120 mg of raloxifene daily for 6 weeks [89]. Thus, while increased hippocampal activity is related to poor performance on traditional cognitive tests of declarative learning and memory in people with schizophrenia [90], on a test of striatal-based non-declarative probabilistic association learning, increased hippocampal activity was related to increased learning, which was consistent with the findings of previous work in patients showing increased hippocampal activity concurrent with better probabilistic association learning [15, 89]. This finding suggests that the human hippocampus represents a neural substrate through which oestrogen receptor stimulation may bring about cognitive benefits in people with schizophrenia, which is consistent with the hippocampus being enriched in oestrogen receptors and being responsive to sex hormones [91, 92]. However, the exact mechanism by which SERMs, such as raloxifene, may work to produce cognitive benefits is presently unknown, and the brain regions potentially benefiting from SERMs, such as raloxifene, may not be restricted to the hippocampus. Additionally, we found that raloxifene administered at 120 mg daily as an adjunct to antipsychotics in men and women with schizophrenia was well tolerated, with no serious adverse events related to the treatment, and the compliance rate was high. This suggests that treatment with SERMs, and raloxifene in particular, may have real clinical potential and warrants further study of these agents as a treatment for cognitive deficits in schizophrenia. However, while early evidence suggests that raloxifene may be useful to improve attention, memory, learning and the associated brain activity in chronically ill men and women with schizophrenia, this inference is based on a limited number of randomized controlled clinical trials that recruited different cohorts of patients in terms of age and gender ratios, administered different doses and assessed a limited range of cognitive abilities.

4 Conclusions

Cognitive deficits are common in schizophrenia, and these cognitive deficits are related to functional impairment, which represents a major obstacle to full recovery. At present, no effective pharmacological treatments are available to reverse the cognitive deficits associated with schizophrenia. However, there is evidence that supports a role of sex hormones and oestrogen in cognitive processing in people with schizophrenia, and some randomized, controlled trials of oestrogen-based treatments have generally shown promising effects (with substantial effect sizes) towards reversing some of the debilitating cognitive deficits in both men and women with schizophrenia and schizoaffective disorder. While many studies have focused on determining the neuroprotective actions of oestrogens, far less is known about SERMs' (specifically raloxifene's) mechanism of action in the brain. There is also some evidence indicating that SERMs and oestradiol act differently [93]. While the initial clinical studies provide hope, identifying the exact mechanism through which SERMs, such as raloxifene, may work (e.g. possibly through reducing inflammation) to bring about reversal of cognitive deficits in schizophrenia may provide even more effective treatments for schizophrenia.

Compliance with Ethical Standards

Funding This work was supported by the School of Psychiatry, University of New South Wales; Neuroscience Research Australia; and the Schizophrenia Research Institute, utilising infrastructure funding from the New South Wales Ministry of Health and the Macquarie Group Foundation. An Australian National Health and Medical Research Council (NHMRC) Senior Research Fellowship (#1021970) supported C. Shannon Weickert. Support for open access charges were funded by the University of New South Wales.

Conflict of interest T W. Weickert, K. M. Allen and C. S. Weickert declare that they have no conflict of interest in relation to this work.

References

1. Green MF. What are the functional consequences of neurocognitive deficits in schizophrenia? Am J Psychiatry. 1996;153:321–30.
2. Weickert TW, Goldberg TE, Gold JM, Bigelow LB, Egan MF, Weinberger DR. Cognitive impairments in patients with schizophrenia displaying preserved and compromised intellect. Arch Gen Psychiatry. 2000;57:907–13.
3. Goldberg TE, Torrey EF, Gold JM, Bigelow LB, Ragland RD, Taylor E, Weinberger DR. Genetic risk of neuropsychological impairment in schizophrenia: a study of monozygotic twins discordant and concordant for the disorder. Schizophr Res. 1995;17:77–84.
4. Donohoe G, Clarke S, Morris D, Nangle JM, Schwaiger S, Gill M, Corvin A, Robertson IH. Are deficits in executive sub processes simply reflecting more general cognitive decline in schizophrenia? Schizophr Res. 2006;85(1–3):168–73.
5. Wells R, Swaminathan V, Sundram S, Weinberg D, Bruggemann J, Jacomb I, Cropley V, Lenroot R, Pereira AM, Zalesky A, Bousman C, Pantelis C, Weickert CS, Weickert TW. The impact of pre-morbid and current intellect in schizophrenia: cognitive, symptom and functional outcomes. NPJ Schizophr. 2015;1:15043. doi:10.1038/npjschz.2015.43.
6. Woodward ND, Heckers S. Brain structure in neuropsychologically defined subgroups of schizophrenia and psychotic bipolar disorder. Schizophr Bull. 2015;41(6):1349–59. doi:10.1093/schbul/sbv048.

7. Joyce EM, Sutton SB, Mutsatsa SH, Barnes TRE. Cognitive heterogeneity in first episode schizophrenia. Br J Psychiatry. 2005;187:516–22.
8. Leeson VC, Barnes TRE, Harrison M, Matheson E, Harrison I, Mutsatsa SH, Ron MA, Joyce EM. The relationship between IQ, memory, executive function and processing speed in recent onset psychosis: one year stability and clinical outcome. Schizophr Bull. 2010;36:400–9.
9. Leeson VC, Sharma P, Harrison M, Ron MA, Barnes TRE, Joyce EM. IQ trajectory, cognitive reserve and clinical outcome following a first episode of psychosis: a 3 year longitudinal study. Schizophr Bull. 2011;37:768–77.
10. Squire LR, Zola SM. Structure and function of declarative and nondeclarative memory systems. Proc Natl Acad Sci USA. 1996;93:13515–22.
11. Keri S, Kelemen O, Szekeres G, Bagoczky N, Erdelyi R, Antal A, Benedek G, Janka Z. Schizophrenics know more than they can tell: probabilistic classification learning in schizophrenia. Psychol Med. 2000;30:149–55.
12. Weickert TW, Goldberg TE, Egan MF, Apud JA, Meeter M, Myers CE, Gluck MA, Weinberger DR. Relative risk of probabilistic category learning deficits in patients with schizophrenia and their siblings. Biol Psychiatry. 2010;67:948–55.
13. Poldrack RA, Clark J, Pare-Blagoev EJ, Shohamy D, Cresco Moyano J, Myers C, Gluck MA. Interactive memory systems in the human brain. Nature. 2001;414:546–50.
14. Fera F, Weickert TW, Goldberg TE, Tessitore A, Hariri A, Das S, Lee S, Zoltick B, Meeter M, Myers CE, Gluck MA, Weinberger DR, Mattay VS. Neural mechanisms underlying probabilistic category learning in normal aging. J Neurosci. 2005;25(49):11340–8.
15. Weickert TW, Goldberg TE, Callicott JH, Chen Q, Apud JA, Das S, Zoltick BJ, Egan MF, Meeter M, Myers C, Gluck MA, Weinberger DR, Mattay VS. Neural correlates of probabilistic category learning in patients with schizophrenia. J Neurosci. 2009;29(4):1244–54.
16. Nuechterlein KH, Subnotnik KL, Green MF, Ventura J, Asarnow RF, Gitlin MJ, Yee CM, Gretchen-Doorly D, Mintz J. Neurocognitive predictors of work outcome in recent onset schizophrenia. Schizophr Bull. 2011;37(Suppl 2):S33–40.
17. Hoe M, Nakagami E, Green MF, Brekke JS. The casual relationships between neurocognition, social cognition and functional outcome over time in schizophrenia: a latent difference score approach. Psychol Med. 2012;42:2287–99.
18. Harvey PD, Heaton RK, Carpenter WT Jr, Green MF, Gold JM, Schoenbaum M. Functional impairment in people with schizophrenia: focus on employability and eligibility for disability compensation. Schizophr Res. 2012;140:1–8.
19. Keefe RSE, Meltzer HA, Dgetluck N, Gawryl M, Koenig G, Moebius HJ, Lombardo I, Hilt DC. Randomized, double-blind, placebo-controlled study of encenicline an α-7 nicotinic acetylcholine receptor agonist as a treatment for cognitive impairment for schizophrenia. Neuropsychopharmacology. 2015. doi:10.1038/npp.2015.176.
20. Pietzak RH, Olver J, Norman T, Piskulic D, Maruff P, Snyder PJ. A comparison of the CogState schizophrenia battery and the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) battery in assessing cognitive impairment in chronic schizophrenia. J Clin Exp Neuropsychol. 2009;31:848–59.
21. Nuechterlein KH, Green MF, Kern RS, Baade LE, Barch DM, Cohen JD, Essock S, Fenton WS, Frese FJ 3rd, Gold JM, Goldberg T, Heaton RK, Keefe RSE, Kraemer H, Mesholam-Gately R, Seidman LJ, Stover E, Weinberger DR, Young AS, Zalcman S, Marder SR. The MATRICS consensus cognitive battery, part 1: test selection, reliability, and validity. Am J Psychiatry. 2008;165:203–13.
22. Minzenberg MJ, Yoon JH, Cheng Y, Carter CS. Sustained modafinil treatment effects on control related gamma oscillatory power in schizophrenia. Neuropsychopharmacology. 2015. doi:10.1038/npp.2015.271.
23. Michalopoulou PG, Lewis SW, Drake RJ, Reichenberg A, Emsley R, Kalpakidou AK, Lees J, Bobin T, Gilleen JK, Pandina G, Applegate E, Wykes T, Kapur S. Modafinil combined with cognitive training: pharmacological augmentation of cognitive training in schizophrenia. Eur Neuropsychopharm. 2015;25:1178–89.
24. Hoff AL, Kremen WS, Wieneke MH, Lauriello J, Blankfeld HM, Faustman WO, Csemansky JG, Nordahl TE. Association of estrogen levels with neuropsychological performance in women with schizophrenia. Am J Psychiatry. 2001;158:1134–9.
25. Ko JH, Joe SH, Cho W, Park JH, Lee JJ, Jung IK, Kim L, Kim SH. Effect of hormone replacement therapy on cognitive function in women with chronic schizophrenia. Intl J Psychiatry Clin Pract. 2006;10:97–104.
26. Mendrek A, Lakis N, Jimenez J. Associations of sex steroid hormones with cerebral activations during mental rotation in men and women with schizophrenia. Psychoneuroendocrinology. 2011;36:1422–6.
27. Fillman SG, Cloonan N, Catts VS, Miller LC, Wong J, McCrossin T, Cairns M, Weickert CS. Increased inflammatory markers identified in the dorsolateral prefrontal cortex of individuals with schizophrenia. Mol Psychiatry. 2013;18(2):206–14.
28. Fillman SG, Sinclair D, Fung SJ, Webster MJ, Weickert CS. Markers of inflammation and stress distinguish subsets of individuals with schizophrenia and bipolar disorder. Trans Psychiatry. 2014;4:e365.
29. Fillman SG, Weickert TW, Lenroot RK, Catts SV, Bruggemann JM, Catts VS, Weickert CS. Elevated peripheral cytokines characterize a subgroup of people with schizophrenia displaying poor verbal fluency and reduced Broca's area volume. Mol Psychiatry. 2015. doi:10.1038/mp.2015.90.
30. Gilmore JH, Fredrik Jarskog L, Vadlamudi S, Lauder JM. Prenatal infection and risk for schizophrenia: IL-1β, IL-6 and TNF-α inhibit cortical neural dendrite development. Neuropsychopharmacology. 2004;29:1221–9.
31. Nguyen KT, Deak T, Owens SM, Kohno T, Fleshner M, Watkins LR, Maier SF. Exposure to acute stress induces brain interleukin-1β protein in the rat. J Neurosci. 1998;18:2239–46.
32. Koo JW, Duman RS. IL-1β is an essential mediator of the antineurogenic and anhedonic effects of stress. Proc Natl Acad Sci USA. 2008;105:751–6.
33. Goshen I, Yirmiya R. Interleukin-1 (IL-1): a central regulator of stress responses. Front Neuroendocrinol. 2009;30:30–45.
34. Bebo BF Jr, Dehghani B, Foster S, Kurniawan A, Lopez FJ, Sherman LS. Treatment with selective estrogen receptor modulators regulates myelin specific T-cells and supresses experimental autoimmune encephalomyelitis. Glia. 2009;57:777–90.
35. Esposito E, Iacono A, Raso GM, Pacilio M, Coppola A, Di Carlo R, Meli R. Raloxifene, a selective estrogen receptor modulator, reduces carrageenan-induced acute inflammation in normal and ovariectomized rats. Endocrinology. 2005;146:3301–8.
36. Gameiro CM, Romao F, Castelo-Branco C. Menopause and aging: changes in the immune system—a review. Maturitas. 2010;67:316–20.
37. Kasai Y, Maegawa M, Yamamoto S, Kamada M, Yasui T, Uemura H, Kobayashi A, Kaneyama M, Tani A, Matsui S, Kuwahara A, Matsuzaki T, Furumoto H, Irahara M. Effects of raloxifene on the production of cytokines in stimulated whole blood in ex vivo and in vitro studies. J Med Invest. 2011;58:110–7.

38. Kumru S, Yildiz FM, Godekmerdan A, Kutlu S, Yilmaz B, Gurates B. Effects of raloxifene and hormone replacement therapy on serum Th2 and Th3 type cytokine concentrations in healthy postmenopausal women: a randomized control trial. Arch Gynecol Obstet. 2008;277:489–93.
39. Lee SA, Bark SH, Kim BC. Raloxifene, a selective estrogen receptor modulator, inhibits lipopolysaccharide-induced nitric oxide production by inhibiting the phosphatidylinositol 3-kinase/Akt/nuclear-kappa B pathway in RA W264.7 macrophage cells factor. Mol Cells. 2008;26:48–52.
40. Levkovitz Y, Mendlovich S, Riwkes S, Braw Y, Levkovitch-Verbin H, Gal G, Fenning S, Treves I, Kron S. A double-blind, randomized study of minocycline for the treatment of negative and cognitive symptoms in early-phase schizophrenia. J Clin Psychiatry. 2010;71(2):138–49.
41. Laan W, Grobbee DE, Selten JP, Heijnen CJ, Kahn RS, Burger H. Adjuvant aspirin therapy reduces symptoms of schizophrenia spectrum disorders: results from a randomized, double-blind, placebo-controlled trial. J Clin Psychiatry. 2010;71(5):520–7.
42. Hafner H. Gender differences in schizophrenia. Psychoneuroendocrinology. 2003;28:17–54.
43. Moore L, Kyaw M, Vercammen A, Lenroot R, Kulkarni J, Curtis J, O'Donnell M, Carr VJ, Weickert CS, Weickert TW. Serum testosterone levels are related to cognitive function in men with schizophrenia. Psychoneuroendocrinology. 2013;18:1185–92.
44. Vercammen A, Skilleter AJ, Lenroot R, Catts SV, Weickert CS, Weickert TW. Testosterone is inversely related to brain activity during emotional inhibition in schizophrenia. PloS One. 2013;8:e77496.
45. Ji E, Weickert CS, Lenroot R, Catts SV, Vercammen A, White C, Gur RE, Weickert TW. Endogenous testosterone levels are associated with neural activity in men with schizophrenia during emotional face processing. Behav Brain Res. 2015;286:338–46.
46. Morris RW, Purves-Tyson TD, Weickert CS, Rothmond D, Lenroot R, Weickert TW. Testosterone and reward prediction errors in healthy men and men with schizophrenia. Schizophr Res. 2015;168(3):649–60. doi:10.1016/j.schres.2015.06.030.
47. Akhondzadeh S, Rezaei F, Larijani B, Nejatisafa A-A, Kashani L, Abbasi SH. Correlation between testosterone gonadotropins and prolactin and severity of negative symptoms in male patients with chronic schizophrenia. Schizophr Res. 2006;84:405–10.
48. Huber TJ, Tettenborn C, Leifke E, Emrich H. Sex hormones in psychotic men. Psychoneuroendocrinology. 2005;30:111–4.
49. Taherianfard M, Shariaty M. Evaluation of serum steroid hormones in schizophrenia patients. Indian J Med Sci. 2004;58:3–9.
50. van Rijn S, Aleman A, de Sonneville L, Sprong M, Ziermans T, Schothorst P, Swaab H. Neuroendocrine markers of high risk for psychosis: salivary testosterone in adolescent boys with prodromal symptoms. Psychol Med. 2006;1:1–8.
51. Perlman WR, Tomaskovic-Crook E, Montague DM, Webster MJ, Rubinow DR, Kleinman JE, Weickert CS. Alteration in estrogen receptor alpha mRNA levels in frontal cortex and hippocampus of patients with major mental illness. Biol Psychiatry. 2005;58:812–24.
52. Weickert CS, Miranda-Angulo AL, Wong J, Perlman WR, Ward SE, Radhakrishna V, Straub RE, Weinberger DR, Kleinman JE. Variants in the estrogen receptor alpha gene and its mRNA contribute to risk for schizophrenia. Hum Mol Genet. 2008;17:2293–309.
53. Gould E, Woolley CS, Frankfurt M, McEwen BS. Gonadal steroids regulate dendritic spine density in hippocampal pyramidal cells in adulthood. J Neurosci. 1990;10(4):1286–91.
54. Woolley CS, Gould E, Frankfurt M, McEwen BS. Naturally occurring fluctuation in dendritic spine density on adult hippocampal pyramidal neurons. J Neurosci. 1990;10(12):4035–9.
55. Bimonte HA, Denenberg VH. Estradiol facilitates performance as working memory load increases. Psychoneuroendocrinology. 1999;24(2):161–73.
56. Daniel JM, Fader AJ, Spencer AL, Dohanich GP. Estrogen enhances performance of female rats during acquisition of a radial arm maze. Horm Behav. 1997;32(3):217–25.
57. Fader AJ, Johnson PE, Dohanich GP. Estrogen improves working but not reference memory and prevents amnestic effects of scopolamine of a radial-arm maze. Pharmacol Biochem Behav. 1999;62(4):711–7.
58. Gibbs RB. Estrogen replacement enhances acquisition of a spatial memory task and reduces deficits associated with hippocampal muscarinic receptor inhibition. Horm Behav. 1999;36(3):222–33.
59. Leuner B, Mendolia-Loffredo S, Shors TJ. High levels of estrogen enhance associative memory formation in ovariectomized females. Psychoneuroendocrinology. 2004;29(7):883–90.
60. Wide JK, Hanratty K, Ting J, Galea LA. High level estradiol impairs and low level estradiol facilitates non-spatial working memory. Behav Brain Res. 2004;155(1):45–53.
61. Tuscher JJ, Fortress AM, Kim J, Frick KM. Regulation of object recognition and object placement by ovarian sex steroid hormones. Behav Brain Res. 2015;285:140–57.
62. Chesler EJ, Juraska JM. Acute administration of estrogen and progesterone impairs the acquisition of the spatial Morris water maze in ovariectomized rats. Horm Behav. 2000;38(4):234–42.
63. Warren SG, Juraska JM. Spatial and nonspatial learning across the rat estrous cycle. Behav Neurosci. 1997;111(2):259–66.
64. Barnes P, Staal V, Muir J, Good MA. 17-Beta estradiol administration attenuates deficits in sustained and divided attention in young ovariectomized rats and aged acyclic female rats. Behav Neurosci. 2006;120(6):1225–34.
65. Voytko ML. Estrogen and the cholinergic system modulate visuospatial attention in monkeys (*Macaca fascicularis*). Behav Neurosci. 2002;116(2):187–97.
66. Yaffe K, Sawaya G, Lieberburg I, Grady D. Estrogen therapy in postmenopausal women: effects on cognitive function and dementia. JAMA. 1998;279:688–95.
67. Mulnard RA, Cotman CW, Kawas C, van Dyck CH, Sano M, Doody R, Koss E, Pfeiffer E, Jin S, Garnst A, Grundman M, Thomas R, Thal LJ. Estrogen replacement therapy for treatment of mild to moderate Alzheimer's disease: a randomized, controlled trial. Alzheimer's Disease Cooperative Study. JAMA. 2000;283:1001–15.
68. Sherwin BB. Estrogen therapy: is time of initiation critical for neuroprotection? Nat Rev Endocrinol. 2009;5:620–7.
69. Shumaker SA, Legault C, Kuller L, Rapp SR, Thal L, Lane DS, Fillit H, Stefanick ML, Hendrix SL, Lewis CE, Masaki K, Coker LH. Women's Health Initiative Memory Study Investigators. Conjugated equine estrogens and incidence of probable dementia and mild cognitive impairment in postmenopausal women. JAMA. 2004;291:2947–58.
70. Lawrence SE, Faught KA, Vethamuthu J, Lawson ML. Beneficial effects of raloxifene and tamoxifen in the treatment of pubertal gynecomastia. J Pediatr. 2004;145:71–6.
71. Landry M, Levesque D, Di Paolo T. Estrogenic properties of raloxifene but not tamoxifen on D2 and D3 dopamine receptors in the rat forebrain. Neuroendocrinology. 2002;76:214–22.
72. Bethea CL, Mirkes SJ, Su A, Michelson D. Effects of oral estrogen, raloxifene and arzoxifene on gene expression in serotonin neurons of macaques. Psychoneuroendocrinology. 2002;27(4):431–45.
73. Cyr M, Landry M, Di Paolo T. Modulation by estrogen-receptor directed drugs of 5-hydroxytryptamine-2A receptors in rat brain. Neuropsychopharmacology. 2000;23(1):69–78.
74. Purves-Tyson TD, Boerrigter D, Allen K, Zavitsanou K, Karl T, Djunaidi V, Double KL, Desai R, Handelsman DJ, Weickert CS. Testosterone attenuates and the selective estrogen receptor modulator, raloxifene, potentiates amphetamine induced locomotion in male rats. Horm Behav. 2015;70:73–84.

75. Goekoop R, Duschek EJ, Knol DL, Barkhof F, Netelenbos C, Scheltens P, Rombouts SA. Raloxifene exposure enhances brain activation during memory performance in healthy elderly males: its possible relevance to behaviour. NeuroImage. 2005;25:63–75.
76. Goekoop R, Barkhof F, Duschek EJ, Netelenbos C, Knol DL, Scheltens P, Rombouts SA. Raloxifene treatment enhances brain activation during recognition of familiar items: a pharmacological fMRI study in healthy elderly males. Neuropsychopharmacology. 2006;31:1508–18.
77. Yaffe K, Krueger K, Cummings SR, Blackwell T, Henderson VW, Sarkar S, Ensrud K, Grady D. Effect of raloxifene on prevention of dementia and cognitive impairment in older women: the Multiple Outcomes of Raloxifene Evaluation (MORE) randomized trial. Am J Psychiatry. 2005;162:683–90.
78. Bergemann N, Parzer P, Jaggy S, Auler B, Mundt C, Maier-Braunleder S. Estrogen and comprehension of metamorphic speech in women suffering from schizophrenia: results of a double-blind, placebo-controlled trial. Schizophr Bull. 2008;34:1172–81.
79. Kulkarni J, Gavrilidis E, Wang W, Worsley R, Fitzgerald PB, Gurvich C, Van Rheenen T, Berk M, Burger H. Estradiol for treatment resistant schizophrenia: a large scale, randomized controlled trial in women of child bearing age. Mol Psychiatry. 2015;20:695–702.
80. Wilk CM, Gold JM, Bartko JJ, Dickerson F, Fenton WS, Knable M, Randolph C, Buchanan RW. Test–retest stability of the repeatable battery for the assessment of neuropsychological status in schizophrenia. Am J Psychiatry. 2002;159:838–44.
81. Ritsner MS, Gibel A, Ram E, Maayan R, Weizman A. Alterations in DHEA metabolism in schizophrenia: two month case control study. Eur Neuropsychopharmacol. 2006;16:137–46.
82. 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, cross-over trial. J Clin Psychopharmacol. 2006;26:495–9.
83. Ritsner MS, Gibel A, Shleifer T, Boguslavsky I, Zayed A, Maayan R, Weizman A, Lerner V. Pregnenolone and dehydroepiandrosterone as an adjunctive treatment in schizophrenia and schizoaffective disorder: an 8 week, double blind, randomized, controlled, 2 center, parallel group trial. J Clin Psychiatry. 2010;71:1351–62.
84. Strous RD, Stryjer R, Maayan R, Gal G, Viglin D, Katz E, Eisner D, Weizman A. Analysis of clinical symptomatology, extrapyramidal symptoms and neurocognitive dysfunction following dehydroepiandrosterone (DHEA) administration in olanzapine treated schizophrenia patients: a randomized, double blind, placebo controlled trial. Psychoneuroendocrinology. 2007;32:96–105.
85. Kulkarni J, Gurvich C, Lee SJ, Gilbert H, Gavrilidis E, de Castella A, Berk M, Dodd S, Fitzgerald PB, Davis SR. Piloting the effective therapeutic dose of adjunctive selective estrogen receptor modulator treatment in postmenopausal women with schizophrenia. Psychoneuroendocrinology. 2010;35(8):1142–7.
86. Usall J, Huerta-Ramos E, Iniesta R, Cobo J, Araya S, Roca M, Serrano-Blanco A, Teba F, Ochoa S. Raloxifene as an adjunctive treatment for postmenopausal women with schizophrenia: a double-blind, randomized, placebo-controlled trial. J Clin Psychiatry. 2011;72(11):1552–7.
87. Huerta-Ramos E, Iniesta R, Ochoa S, Cobo J, Miguel E, Roca M, Serrano-Blanco A, Teba F, Usall J. Effects of raloxifene on cognition in post-menopausal women with schizophrenia: a double-blind, randomized, placebo-controlled trial. Eur Neuropsychopharmacol. 2014;24:223–31.
88. Weickert TW, Weinberg D, Lenroot R, Catts SV, Wells R, Vercammen A, O'Donnell M, Galletly C, Liu D, Balzan R, Short B, Pellen D, Curtis J, Carr VJ, Kulkarni J, Schofield PR, Weickert CS. Adjunctive raloxifene treatment improves attention and memory in men and women with schizophrenia. Mol Psychiatry. 2015;20:685–94.
89. Kindler J, Weickert CS, Skilleter AJ, Catts SV, Lenroot R, Weickert TW. Selective estrogen receptor modulation increases hippocampal activity during probabilistic association learning in schizophrenia. Neuropsychopharmacology. 2015;40:2388–97.
90. Tregellas JR, Smucny J, Harris JG, Olincy A, Maharajh K, Kronberg E, Eichman LC, Lyons E, Freedman R. Intrinsic hippocampal activity as a biomarker for cognition and symptoms in schizophrenia. Am J Psychiatry. 2014;171:549–56.
91. Shughrue PJ, Merchenthaler I. Evidence for novel estrogen binding sites in the rat hippocampus. Neuroscience. 2000;99(4):605–12.
92. Woolley CS. Estrogen-mediated structural and functional synaptic plasticity in the female rat hippocampus. Horm Behav. 1998;34(2):140–8.
93. Ciriza I, Carrero P, Azcoitia I, Lundeen SG, Garcia-Segura LM. Selective estrogen receptor modulators protect hippocampal neurons from kainic acid excitotoxicity: differences with the effect of estradiol. J Neurobiol. 2004;61(2):209–21.