LEADING ARTICLE

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

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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 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, 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.

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.

| 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

△ Adis
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 differentially [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

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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.

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