Memory impairment in female schizophrenic patients and its relation with their female sex hormonal profile

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Hypothesis
Schizophrenic women show deficits in a variety of cognitive domains including executive function, attention, memory, and language. The female sex hormone estrogen acts as a neuroactive hormone that is assumed to have interesting effects on the central nervous system and on the cognitive functions in specific.

Aim of the work
To determine the memory impairment in a sample of schizophrenic female patients, as well as its relation to the level of their female sex hormone estradiol, to evaluate the usefulness of hormonal therapy as an adjunct therapy to antipsychotic drugs in female schizophrenic patients to improve their cognitive functions.

Participants and methods
This is a comparative study that included 30 schizophrenic female patients who were admitted for a long time as inpatients of Al Abasseia Psychiatric Hospital, and a control group that matched in age and education. They were subjected to a psychiatric interview, neurological examination, general examination, the scale for the assessment of positive symptoms, and scale for the assessment of negative symptoms, serum estradiol level during 3 consecutive weeks, and the Luria–Nebraska neuropsychological battery, which is a multidimensional battery designed to assess a broad range of neuropsychological functions. (We focused on the items that tested memory functions).

Results
There were statistically significant differences between both groups in the clinical scales C10 (memory) of the Luria–Nebraska neuropsychological battery, as well the factor scales concerned with memory ME1 (verbal memory) and ME2 (visual and complex memory). The mean estradiol level was inversely correlated with the mean of the memory scales; that is, an increased estradiol level was correlated with better performance of the patient group in memory scales.

Conclusion
Female schizophrenic patients performed significantly worse in the memory scale (C10), as well as the factor scales concerned with memory ME1 (verbal memory) and ME2 (visual and complex memory); the increased estradiol level was correlated with better performance of the patient group in memory scales, which may be of value in these patients when providing hormonal therapy as an adjunct therapy to antipsychotic drugs.

Keywords:
female sex hormones, memory impairment, schizophrenia

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Introduction

Efforts to identify differential or core cognitive deficits in schizophrenia have been made for several decades, with limited success. Part of the difficulty in establishing a cognitive profile in schizophrenia is the considerable interpatient heterogeneity in the level of cognitive impairment. Thus, it may be useful to examine the presence of relative cognitive weaknesses on an intraperson level (Palmer *et al.*, 2010).

Estrogen is a neuroactive hormone that exerts powerful effects on the central nervous system, especially on cognitive functions. The largest concentrations of estrogen receptors-β are in the hypothalamus, the amygdala, and the hippocampus (Shughrue and Merchenthaler, 2000). The neurotransmitter that estrogen upregulates the most is acetylcholine (Luine, 1985), although it affects the serotonergic, noradrenergic, and dopaminergic systems as well (McEwen, 2002). Moreover, the hippocampus itself has been shown to be critical for explicit or declarative memory. Sherwin and McGill (2003) suggested that estrogen may exert the maximum effects on memory, although this does not exclude the possibility that estrogen might influence other cognitive functions as well. Estrogens exert complex and time-dependent effects on spatial and declarative memory in animals

(Voytko, 1996; Fader *et al.*, 1998; Gibbs *et al.*, 1998; Green, 2006).

Also, estrogen has been postulated to have a positive effect on short-term and long-term verbal memory in postmenopausal women, as well as increasing the capacity for new learning (Sherwin and McGill, 2003). Estrogen replacement therapy (ERT) has an added benefit for cognitive deficits in postmenopausal women with schizophrenia (Kulkarni *et al.*, 1996).

Aim of the work

The aim of this study is to determine memory impairment in a sample of schizophrenic female patients, its relation to their positive and negative symptoms, and the level of the female sex hormone estradiol, to evaluate the usefulness of hormonal therapy as an adjunct therapy to antipsychotic drugs, to improve their cognitive functions.

Participants and methods

Participants

This Comparative case–control study was carried on a sample of Egyptian women.

Patient group

This group included 30 patients fulfilling the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, Text Revision diagnostic criteria for schizophrenia that was confirmed by two other psychiatrists.

They were admitted to Al Abasseia Psychiatric Hospital with at least 2 years of illness. They did not show acute exacerbation. They were under treatment either by conventional antipsychotics, atypical antipsychotics, or both. Informed consent was obtained from the general director of the hospital, from the patients, and their relatives.

Control group

The control group included 15 normal women. They were subjected to a clinical assessment, which included a detailed psychiatric interview and neurological and general examinations, with neuropsychological evaluation using the Luria–Nebraska neuropsychological battery (LNNB). Also, the gynecological history was obtained and hormonal assessment was performed. For every case, two blood samples were obtained: one during menstruation and one on days 10–12 of the cycle. The women selected in both groups fulfilled the following criteria:

Inclusion criteria: Women in the child-bearing period.

All patients should continue at least 6 years of education. This was a necessity for completion of the psychological evaluation.

Exclusion criteria: History of taking any synthetic steroids (including oral contraceptive pills) before and during the examination.

Pregnant women and those with ovarian dysfunction or other gynecological problems.

History of neurological illness, epilepsy, head trauma, mental retardation, acute medical illness, or substance abuse.

Uncooperative patients.

History of electro convulsive therapy application in the previous 6 weeks before examination.

Methods

Clinical assessment

(1) Psychiatric interview: the semistructured sheet of the psychiatric department of Al Kasr El-Aini Hospital, Faculty of Medicine, Cairo University was used for the psychiatric interview of the patients.
(2) Neurological examination.
(3) General examination.

Psychiatric symptoms rating

The scale for the assessment of positive symptoms (SAPS) and the scale for the assessment of negative symptoms (SANS) were used (Andreasen, 1984a).

Hormonal assessment

To assess the serum level of estradiol, three blood samples were taken on 3 consecutive weeks (not two samples) to nullify the effect of menstrual irregularities. The hormonal assessment was performed at Kasr El-Aini university hospital, the laboratory of the Obstetric and Gynecology Department. The normal estradiol ranges were as follows: the follicular phase (30–50 pg/ml), periovulatory (150–450 pg/ml), the luteal phase (150–230 pg/ml), and postmenopausal (0–25 pg/ml).

Neuropsychological assessment

LNNB (Golden *et al.*, 1995) is a multidimensional battery designed to assess a broad range of neuropsychological functions.

Adaptation to the Arabic version was performed accurately with the agreement of professional judgments (one senior psychiatrist and one senior psychologist). The reliability of the LNNB has been examined from a number of perspectives including interrater agreement, split-half, internal consistency, and test–retest reliability, and proven to be reliable. Also, criterion-related, concurrent, and construct validity of the LNNB has been proven. We focused on items that tested memory:

Clinical scales: C10-memory; this scale basically tests short-term and intermediate memory.

Factor scales: the factor scales resulted from a series of studies in which each of the major scales of the test

Table 1 Age and educational level

	Patient group		Control group
Mean age ± SD	34.6 ± 6.8		34.6 ± 6.7
P		0.99	
Mean years of education ± SD	12.6 ± 2		12.67 ± 1.98
P		0.96	

Table 2 The scale for assessment of positive symptoms, the scale for assessment of negative symptoms

SAPS	No.	Mean ± SD	SANS	No.	Mean ± SD
Delusions	30	33.6 ± 10.1	Affective flattening or blunting	30	19.97 ± 4.8
Positive formal thought disorder	30	18.97 ± 8.2	Anhedonia-asociality	30	15.8 ± 3.8
Hallucinations	30	13.9 ± 5.8	Avolition-apathy	30	11.0 ± 2.03
Bizarre behavior	30	12.2 ± 3.2	Alogia	30	10.5 ± 4.6
Inappropriate affect	30	3.1 ± 0.8	Attention	30	7.87 ± 2.5
Total SAPS	30	81.7 ± 20.4	Total SANS	30	64.8 ± 13.7

SANS, scale for assessment of negative symptoms; SAPS, scale for assessment of positive symptoms.

Table 3 The three estradiol levels

Estradiol levels (E2)	Mean ± SD
Follicular phase	
Patients No. = 28	57.4 ± 41.6
Control No. = 15	69.1 ± 22.2
Periovulatory phase	
Patients No. = 30	151.9 ± 110.1
Control No. = 15	181.5 ± 131.8
Mean of estradiol levels in both phases	
Patients No. = 30	112 ± 89.3
Control No. = 15	125.3 ± 69.1

Table 4 The results of Luria–Nebraska neuropsychological battery in both patient and control groups

Group	Number	Mean ± SD	*P*
C10 (memory)			
Patients	30	72.52 ± 10.2	0.000*
Control	15	43.80 ± 4.2	

*Significant $P < 0.05$.

Table 5 Factor scales

Factor scale	Group	Number	Mean ± SD	*P*
ME1(verbal memory)	Patients	30	76 ± 7.95	0.000*
	Control	15	53.8 ± 5.2	
ME2(visual and complex memory)	Patients	30	62.6 ± 8.04	0.000*
	Control	15	44.6 ± 4.7	

*Significant $P < 0.05$.

Table 6 Correlation of the mean E2 and clinical scales: E2 and C10 (memory)

	Total number	*R*	*P*
Patients	30	−0.380	0.038*
Control	15	−0.106	0.707

*Significant $P < 0.05$.

Table 7 Correlation of the mean E2 and factor scales

LNNB scales	Group	Total No.	*R*	*P*
ME1(verbal memory)	Patients	30	−0.766*	0.027*
	Control	15	−0.547*	0.035*
ME2 (visual and complex memory)	Patients	30	−0.585*	0.012*
	Control	15	−0.877*	0.000*

LNNB, Luria–Nebraska neuropsychological battery.
*Significant $P < 0.05$.

Table 8 Correlation of E2 (mean estradiol levels) and scale for assessment of positive symptoms and the scale for assessment of negative symptoms

	No.	*R*	*P*
SAPS			
Hallucinations	30	−0.098	0.61
Delusions	30	−0.113	0.55
Bizarre behavior	30	0.166	0.382
Positive formal thought disorder	30	−0.004	0.98
Inappropriate affect	30	0.227	0.227
Total SAPS	30	−0.051	0.790
SANS			
Affective flattening or blunting	30	0.014	0.93
Alogia	30	0.150	0.43
Avolition-apathy	30	0.118	0.54
Anhedonia-asociality	30	−0.212	0.26
Attention	30	−0.072	0.71
Total SANS	30	0.009	0.96

SANS, scale for assessment of negative symptoms; SAPS, scale for assessment of positive symptoms.

battery was investigated in separate factor analyses (Golden *et al.*, 1995).

(1) ME1 (verbal memory). These items involve recalling lists of words presented visually and orally. These items require short-term verbal memory skills.
(2) ME2 (visual and complex memory). These items involve drawing shapes, copying hand positions, repeating stories, and repeating words associated with pictures, all from memory. They require short-term memory for visual stimuli, memory for combined verbal and visual information, and integration of visual memory with motor skills.

Statistical techniques used

Percentages, means, and SD were calculated. A *t*-test and Pearson correlation were also performed using the SPSS (version 11, IBM, Armonk, New York, USA) analysis computer program (Table 1).

Results

Demographic and clinical data

There were no statistically significant differences between both groups in terms of the mean age and the mean years of education.

Occupation, marital status, family history, and history of menstrual disturbance: there was a higher percentage of working women in the control group in comparison with 80% nonworking schizophrenic patients. Also, most of them were married in contrast to more single and divorced schizophrenic patients. 36.7% of schizophrenic patients had

menstrual irregularities compared with none in the control group. 53.3% of schizophrenic patients had a family history of psychosis in contrast to 6.7% in the control group.

Table 2 shows that delusions and positive formal thought disorders were the most common positive symptoms in our patients. Also, affective flattening or blunting and anhedonia-asociality were the most common negative symptoms in the patient group.

Hormonal assessment

Results of serum estradiol measurements: for the patient and control groups, the first samples presented a serum level of estradiol in the follicular phase and the second samples presented a serum level in the periovulatory phase. We excluded two patients as the first samples were more than 300 pg/ml. Thus, these samples did not represent the follicular phase in those patients. The serum estradiol levels measured in the third samples for the patient group were only used when assessing the correlation of estradiol level and different scales of LNNB.

Table 3 shows that the mean serum estradiol level in all phases was higher in the control group than that in the patient group.

The critical level

The critical level represents the highest LNNB score, which can be considered normal for the battery and is adjusted for both age and education. Thus, scores above the critical level are considered impaired and scores below this level are considered normal. The critical level represents the cutoff point in other tests; it was 57.76 ± 3.28 in the patient group in contrast to 57.66 ± 3.11 in the control group, and there was no significant difference between the patient and the control group as *P*-value was greater than 0.05. This is very important for comparison of both.

Clinical scales

Table 4 also shows that there were statistically significant differences between the patient and control groups in the performance of C10 (memory). The patient group performed above the critical levels in this scale and the control group performed below the critical level ,that is, memory is impaired in the patient group and intact in the control group.

Table 5 shows that there were statistically significant differences between the patient and control groups in terms of their performance on factor scales ME1 (verbal memory) and ME2 (visual and complex memory). The patient group performed above the critical levels on these factor scales and the control group performed below the critical level. This means that these functions are impaired in the patient group and intact in the control group.

Results of correlations

Table 6 shows that the mean estradiol level was inversely correlated with the scores of the C10 (memory) in the patient group and this correlation was significant statistically as *P*-value was less than 0.05. This means that a high estradiol level is correlated with good performance of memory function (short-term and intermediate memory) in patients with schizophrenia but not in the control group.

Table 7 shows that the mean estradiol level is inversely correlated with the mean of scales ME1 (verbal memory) and ME2 (visual and complex memory), and this correlation was statistically significant in both the patient and the control group.

Table 8 shows that the mean estradiol levels of the patient group showed no significant correlation between the total SAPS and subscales of SAPS as the *P*-value was greater than 0.05 in all the correlations.

Discussion

This study is a case–control comparative study, with no statistically significant difference regarding age and years spent in education that was necessary in order to be able to complete the LNNB. Low rates of marriage in the patient group could be explained by the effect of the psychotic disorder on the patients' coping mechanisms and the effect of the psychotic disorder on patients' abilities to maintain normal life to maintain the relationship. Also, the early onset of schizophrenia may explain the low rates of marriage in some patients. Our results agree with those of Halari *et al.* (2004), who reported low number of married individuals among schizophrenic patients. The scale for the assessment of positive symptoms (SAPS) and scale for the assessment of negative symptoms (SANS). Andreasen (1984b) mean of total SAPS, delusions subscale, positive formal thought disorder, hallucinations subscale and bizarre behavior subscale were within the range of mild-moderate in severity. The means of total SANS, affective flattening or the blunting subscale of SANS, the Anhedonia-asociality subscale, the avolition-apathy subscale of SANS, the alogia subscale, and the attention subscale were within the range of mild-moderate severity. The scores of SAPS were inversely correlated with the scores of SANS. Thus, the means of SAPS and SANS for all the patients were in the mild to moderate range. Another explanation was that we excluded patients with marked to severe positive or negative symptoms, who may not be cooperative during the cognitive assessment. As regards the results of the hormonal assessment, the mean serum estradiol levels in the follicular phase, periovulatory, and both phases for the patient group were lower than those of the control group.

We considered patients to have hypoestrogenism when they had a serum estradiol level below 30 pg/ml in the follicular phase and/or below 150 pg/ml in the luteal or periovulatory phase according to the laboratory of Obstetric and Gynecology Department at Kasr El-Aini university hospital. Thus, all the control cases were within normal levels. Five patients had hypoestrogenism in the follicular phase, nine patients had hypoestrogenism in the luteal or periovulatory phase, and four patients showed hypoestrogenism in both follicular and luteal phases. Thus, a total of 18 patients (60%) showed hypoestrogenism. This result agrees with that reported by Bergemann *et al.* (2005), who found hypoestrogenism

in 57.3% of the patients. Also, our result agrees with Ko *et al.* 2006, who found hypoestrogenism in 62.8% of patients with schizophrenia. There are many explanations for the hypoestrogenism in our study. Most of our patients (96.7%) were on treatment with conventional antipsychotics, which in particular are known to induce hyperprolactinemia, which reduces estrogen levels.

The C10 (memory) scale basically tests short-term and intermediate memory. The study found that the patient group had mean scores of the C10 above the critical level. Also, the patient group performed significantly above the control group on scale C10. This means that schizophrenic patients had significant memory impairment. Also, there were statistically significant differences between the patient and control groups on factor scales: ME1 (verbal memory) and ME2 (visual and complex memory). Thus, impairment in schizophrenic patients involved short-term and intermediate memory, verbal memory, visual, and complex memory. This memory impairment may contribute to the development of the psychopathology of schizophrenia. These results agree with those reported in the literature. Valsharkey *et al.* (2000) reported that impaired memory is a prominent feature of schizophrenia. In general, patients tend to be impaired more on difficult memory tasks that require active processing of materials, whereas procedural learning that involves motor skills may be less impaired. Hoff *et al.* (2001), reported that with age and education controlled, the first-episode and chronic patients with schizophrenia performed significantly worse than the normal participants on neuropsychological summery measures of verbal memory and spatial memory Danion *et al.* (1999), and Kuperberg and Heckers (2000) reported that memory deficits in schizophrenia are associated with an inability to link the separate aspects of events into a cohesive, memorable, and distinctive whole. Also, working memory deficits are well known in schizophrenia (Quintana *et al.*, 2003; Meda *et al.*, 2009; Palmer *et al.*, 2010) Although most of the previous studies did not use the LNNB, it was highly correlated with tests of memory. For example, Buchanan *et al.* (2004) found a correlation between the Wechsler Memory Scale (Wechsler, 1987) and the LNNB C10 scale. They also found a 72% agreement between the scales on identification of memory impairment, and there are many correlation studies on the LNNB and other psychological tests, which are beyond the scope of this discussion. This is important so that we can compare the results from the LNNB with the results of other tests.

In terms of the results of correlations, the study proved that the mean estradiol levels were inversely correlated with the mean performance of the C10 (memory) measuring short-term and intermediate memory, ME1 (verbal memory), and ME2 (visual and complex memory). All these correlations were statistically significant. This means that a high estradiol level is correlated with good performance of memory function (short-term and intermediate memory, verbal memory, visual and complex memory) in patients with schizophrenia but not in the control group.

In our study, the estradiol level was correlated with higher performance on memory. These results agree with those reported by Ko *et al.* (2006) and Hoff *et al.* (2001), who reported that serum estradiol levels showed direct significant correlations with the verbal memory, verbal fluency, and executive functions, and also with Sherwin and McGill (2003), who found that estrogen has a positive effect on short-term and long-term verbal memory in postmenopausal women, as well as increasing the capacity for new learning. However, the study disagrees with Halari *et al.* (2004), who failed to found any correlation of estrogen with any cognitive domains.

Other studies failed to find any effect of estrogen on cognitive functions in postmenopausal women for example: Duff and Hampson (2000) and Janowsky *et al.* (2000). Also, no differences in scores on tests of verbal memory, occurred in women 81 years old treated with either estrogen or progestin compared with those treated with placebo (Binder *et al.*, 2001). Moreover, Barch *et al.* (2003) reported that estrogen plus progestin did not improve cognitive functions in women aged 65 years when compared with placebo. The study of Seeman and Fitzgerald (2000) summarized the possible roles of ERT itself as a hormonal therapy in female patients with schizophrenia, in that estrogen may be a useful addition to antipsychotic medication in terms of downregulating dopaminergic transmission and by its action on the serotonin system. Estrogen helps to ameliorate cyclical symptomatic fluctuations in women with resistant symptoms. It also preserves bone density and prevents cardiovascular disease, especially in menopausal women; also, estrogen may play a role in ameliorating or preventing symptoms of tardive dyskinesia. In addition, it can be used to counter the unwanted hyperprolactinemia effects that may have accompanied a lifetime of treatment with older antipsychotic medication (Kuperberg and Heckers, 2000). Also, Zec and Trivedi (2002) reported that ERT acts to maintain some aspects of cognition in postmenopausal women, especially verbal memory and learning, as their performance was better in 47% of memory measures in women who received ERT. Moreover, across these studies, there was a significantly higher percentage of significant positive findings for the tests of verbal compared with visual memory performance with ERT.

The results of this study should be interpreted in the light of the following limitations: first, we did not include a normal control group with a low estrogen level to compare the results and the specificity of estrogen to memory impairment. Second, our sample was obtained from Alabbasia hospital with a high institutionalization rate with its impact on cognitive functions.

Conclusion

(1) Schizophrenia is associated with a poor work record and low marriage rates.
(2) Female schizophrenic patients had a history of menstrual irregularities more than healthy normal

controls. Sixty percent of schizophrenic patients had hypoestrogenism at some point in their menstrual cycle.

(3) Schizophrenic patients performed significantly worse than the normal healthy controls on the memory scales of the LNNB: clinical scale (C10) and the factor scales: ME1 (verbal memory) and ME2 (visual and complex memory).

(4) Increased estrogen level was correlated with better performance of the patient group, as well as in healthy menstruating women in memory (intermediate-memory and short-term memory), verbal memory, and visual complex memory domains.

(5) The estrogen level is not correlated with positive or negative symptoms of schizophrenia.

Recommendations

(1) Further studies should be conducted to examine the effect of estrogen on other cognitive domains, that is, other memory aspects, for example, working memory, language, intellectual abilities, or on the patient's functioning, quality of life, as we see part of the difficulty in establishing a cognitive profile in schizophrenia is the considerable interpatient heterogeneity in the level of cognitive impairment. Thus, it may be useful to examine the presence of relative cognitive weaknesses at an intraperson level.

(2) A larger sample can be used and unhospitalized patients can also be studied.

(3) Follow-up studies can be conducted for schizophrenic patients after hormonal replacement therapy when indicated and they can be compared with normal women receiving the same hormonal therapy as regards their cognitive abilities in order to examine the benefits of hormonal replacement therapy.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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