Toward a Meta-Analytic Approach of Sex Differences in Episodic Memory of Schizophrenia Patients: Exploratory Findings

Adrianna Mendrek [1], Amir A. Sepehry [1], Emmanuel Stip [1]

Abstract

Studies in the general population have demonstrated the existence of sex differences in cognitive function. In terms of memory, women outperform men on verbal, whereas men exhibit either superior or comparable nonverbal episodic memory. The results obtained in schizophrenia patients have been more variable. The main objective of the present study was to combine available data and perform preliminary analysis of potential differences between men and women with schizophrenia on verbal and nonverbal episodic memory. Systematic electronic literature searches via PubMed, PsychINFO, MEDLINE In-Process and other non-indexed citations, and EMBASE yielded seventy-four articles out of which ten matched our prespecified inclusion and exclusion criteria. The analysis revealed that sex differences in schizophrenia in nonverbal memory function were consistent with that which has been observed in the general population (men outperforming women). In contrast, the nonsignificant effect in verbal memory suggested a loss of normal sexual dimorphism (women outperforming men), possibly due to the differential effect that schizophrenic illness exerts on neurocognitive function in men and women. These preliminary results imply differential effects of schizophrenic illness on men and women, and call for considering sex differences in clinical cognitive trials with medications.

Key Words: Schizophrenia, Sex Differences, Episodic Memory, Cognition, Meta-Analysis, Gender

Introduction

Over the past two decades, studies have consistently shown the existence of sex differences in cognitive function in the general population, with men, on average, performing better on spatial and mathematical reasoning tasks (1-3), and women excelling on tests of verbal fluency and memory (2, 4, 5). In the domain of memory, sex differences have usually been observed in verbal episodic memory, with the superior performance of women when the "to be remembered items" were words, stories or concrete pictures (6-8). In terms of nonverbal episodic memory, either no difference or superior performance has been found in men, particularly when the "to be remembered items" were visuo-spatial in nature (9).

Sex differences in cognitive function have been attributed to organizational (*in utero* and during early brain development) and activational (in adolescence and in adulthood) effects of sex steroid hormones (especially estrogen and testosterone) (10-13). Together with cognition, these hormones also contribute to sex differences in neuroanatomy. Thus,

[1] *Centre de Recherche Fernand-Seguin, Department of Psychiatry, Université de Montréal*

Address for correspondence: Adrianna Mendrek, PhD, Centre de Recherche Fernand-Seguin, Department of Psychiatry, Université de Montréal, 7331 Hochelaga, Montréal (QC) H1N 3V2, Canada
Phone: 514-251-4015, x3528; Fax: 514-251-2617;
E-mail: adrianna.mendrek@umontreal.ca

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compared with men, relative to the cerebrum size, women appear to have relatively larger volumes of regions implicated in language and memory, such as dorsolateral prefrontal cortex, superior temporal cortex and the hippocampus (14, 15), though direct correlations with sex differences in cognitive function are lacking. In terms of functional neuroimaging, the studies of episodic memory typically show left prefrontal activations during encoding, right prefrontal activations during retrieval, and hippocampal activation during both encoding and retrieval (16-19), but no consistent sex differences have been found (20). Nevertheless, several studies have revealed different functional brain lateralization, with females typically exhibiting more bilateral distribution of brain activations during various cognitive tasks (21, 22).

Despite relatively well-established sex differences in the epidemiology and phenomenology of schizophrenia (23), the neuropsychological findings are inconsistent, with some studies pointing to superior performance by female patients, while others demonstrating the opposite effect or no difference between the sexes. For example, Seidman and colleagues (24) have observed that, in comparison to women patients, men with schizophrenia have impaired executive function as assessed by the Wisconsin Card Sorting Test (WCST). Hoff and colleagues (25) have shown that male patients were more impaired than female patients in spatial memory, but this difference was eliminated when disparity in symptom severity between the sexes was controlled. Goldstein and colleagues (26) employed an extensive neuropsychological battery and found that male patients were significantly impaired across all cognitive domains in comparison with normal male subjects and, on tests of attention, verbal memory and executive function, in comparison with female patients. Female patients, on the other hand, performed significantly worse than female normal comparison subjects only on tests of attention, executive function and visual memory, implying that women with schizophrenia may be less vulnerable to verbal processing deficits than men. Similarly, studies focusing specifically on episodic verbal memory (27) have found superior performance in women relative to men with schizophrenia. In contrast, Lewine and colleagues (28) have demonstrated that it was women with schizophrenia who performed significantly worse than men on tasks of verbal memory, spatial memory and visual processing. Finally, several studies have found no difference in cognitive function between men and women with schizophrenia (29-31).

The main objective of the present study was to combine available data concerning sex differences in cognitive function in schizophrenia and perform preliminary meta-analysis. Despite the fact that we carried out a search within all cognitive domains, for the final analysis we included only data for the episodic memory—the memory of unique events (32). We concentrated on this specific function for several reasons, including the facts that: 1) sex differences in episodic memory have been well documented in the general population; 2) the impairments in episodic memory, including both encoding and retrieval, appear to be selective against a background of other cognitive deficits in schizophrenia (33, 34); 3) most existing studies of sex differences in schizophrenia have looked at the episodic memory function; and, 4) the available data were most amenable for further analysis.

Another contributing factor to the rationale of the present study was our recent finding of sex difference in cerebral function in schizophrenia. Overall, the functional neuroimaging studies have shown that performance on episodic memory tasks by patients is associated with disturbed activations in several prefrontal cortical regions, as well as in the temporal-limbic areas including hippocampus (35, 36). Structural neuroanatomical studies have demonstrated that men are characterized by larger ventricles (37) and smaller overall frontal and temporal lobe volumes (38-40) relative to women patients, though not all the studies have found this effect (41, 42). Although there are no reports of sex differences in cerebral function during performance of episodic memory tasks, we have recently found more extensive and intense activations in men relative to women with schizophrenia during emotion processing tasks (43). Despite the fact that we have investigated effect, some of the differences between men and women appeared in prefrontal and temporal-limbic regions, which have also been associated with the episodic memory function.

Our final reasons to perform this preliminary meta-analysis of potential sex differences in episodic memory in schizophrenia include the association of schizophrenia with less lateralized brain function (44-47), as well as the evidence of disturbed levels of sex steroid hormones, such as estrogen and testosterone (48-50), both of which have been implicated in cognitive function (12, 13). Because of the documented sex difference in the general population in terms of verbal and nonverbal episodic memory, we analyzed these separately in schizophrenia patients.

Methods

Search Strategy and Identification of Studies for the Present Analysis

Systematic electronic literature searches via PubMed (all years), EMBASE (1980–2006), MEDLINE In-Process and other non-indexed citations (April 11, 2007), and PsychINFO (1967–week 1 April, 2007) with the key words "schizophrenia" AND ("sex differences" or "gender differences") AND "cognition" have been performed. In addition, the relevant studies were identified from the reference lists of already selected studies. Whenever necessary,

Table 1 Demographic Characteristics of the Studies

Study Authors, Year (Ref #)	N Patients	N Male	Age, Years (SD)	N Female	Age, Years (SD)	N In/Out Patients	Drugs
Albus et al., 1997 (29)	66	37	28.8 (7.1)	29	33.2 (11.2)	In	CE
Fiszdon et al., 2003 (27)	28	17	37.5 (9.2)	11	38.7 (8.8)	Out	NR
Goldberg et al., 1995 (31)	63	41	32.7 (8.3)	22	32.0 (7.0)	Mix	Mix
Goldstein et al., 1998 (26)	31	17	37.0 (5.8)	14	41.6 (7.7)	Out	CE
Gruzelier et al., 1999 (47)	104	66	33.44 (8.13)	38	35.7 (8.45)	Mix	CE
Halari et al., 2004 (51)	37	20	40.45 (10.6)	17	47.76 (9.34)	Mix	CE
Hoff et al., 1998 (25)	132	92	30.95 (7.44)	40	36.09 (8.89)	In	CE
Lewine et al., 1997 (28)	191	130	33.01 (8.29)	61	37.69 (9.53)	Mix	Mix
Ragland et al., 1999 (52)	75	45	NR	30	NR	NR	CE
Sota & Heinrichs, 2003 (53)	106	70	44.7 (NR)	36	38.9 (NR)	Out	MT

CE=chlorpromazine equivalence; NR=not reported; MT=mostly typical antipsychotics

the authors were contacted for further details concerning their data. Studies included in the present meta-analysis involved neurocognitive assessment of potential differences between men and women with schizophrenia-spectrum disorder diagnosis. Only the results obtained with validated rating scales and tests of episodic memory were incorporated into the final analysis.

Demographic Characteristics of Participants in Included Studies

Our quantitative review of memory performance associated with sex differences in schizophrenia consisted of ten studies (25-29, 31, 47, 51-53) (see Table 1). The number of patients enrolled in those studies ranged from 31 to 191 with the total N=833 (535 males and 298 females). With one exception (52), all the studies reported the ages of the male and the female participants separately. In cases of multiple subject groups per study, the mean age and standard deviation (SD) have been calculated via D-Stat (55). Thus, the male mean age ranged from 28.8 (SD=7.1) to 40.45 (SD=10.6), while the female mean age ranged from 32.0 (SD=7.0) to 47.76 (SD=9.34).

Four studies included mixed samples of in- and outpatients (28, 31, 47, 51), two studies consisted of inpatients only (25, 29), and three studies consisted of outpatients only (26, 27, 53). All studies involved medicated populations: six reported chlorpromazine equivalence (25, 26, 29, 47, 51, 52), two tested patients receiving mixed drug type (28, 31), one study mostly typical antipsychotics (53), and one did not control for medication (27).

Statistical Method

Whenever available, means and standard deviations along with the sample sizes, for men and women separately in each study, were used for calculation of the effects. In the absence of this first rank data, we referred to the difference of the means between the sexes reported by the authors as t-tests, z-scores, F values or effect sizes.

Comprehensive Meta-Analysis (CMA) (54) and D-Stat (55) have been used to calculate the effect size estimates. All effect size estimates were calculated for 95% confidence intervals (CIs). Consistent with the hypothesis that females exhibit superior performance on verbal memory tasks, while men perform better on nonverbal memory tasks, for the CMA analysis we assigned a positive direction of the effect when the results of a given study showed a superior performance of women on the verbal memory, and a negative direction of the effect when women performed better on the nonverbal episodic memory. Following selection of appropriate studies, we extracted data pertaining specifically to the episodic memory function (for the memory tests included in the analysis, see Table 2).

Results

Study Search Outcome

After removal of the duplicates from the search engines (PubMed, PsychINFO, MEDLINE In-Process and EMBASE), our database yielded a total number of seventy-four possible abstracts for a meta-analytic evaluation. The thorough screening processes using our inclusion and exclusion criteria yielded ten studies (for demographic and clinical synopsis of these ten studies, refer to Table 1).

Meta-Analytic Outcome Measure

The outcome measure obtained on the verbal episodic memory from aggregating ten studies demonstrated a nonsignificant and heterogeneous effect estimate based on

Table 2 Long-Term Memory (LTM) Scales Used in Calculation of the Effect Estimates

Study Authors, Year (Ref #)	LTM-Verbal	LTM-Nonverbal
Albus et al., 1997 (29)	WMS-R—verbal memory & learning logical-memory-passage immediate-delayed paired associated learning test CVLT—sum of trial 1–5	WMS-R—visual memory visual reproduction-immediate-delayed
Fiszdon et al., 2003 (27)	CVLT—verbal learning-sum of trial 1–5	—
Goldberg et al., 1995 (31)	WMS-R—delay naming WMS-R—verbal Warrington Test—words CVLT—total WMS-R—paired associate WMS-R—logical memory	WMS-R—visual reproduction face recognition Warrington Test—faces
Goldstein et al., 1998 (26)	WMS-R—verbal memory (logical memories, immediate and delayed recall) CVLT—total correct on trial 1–5	WMS-R—nonverbal memory (visual reproduction, immediate and delayed recall-total) WAIS-R—digit symbol recall, free and matched pairs
Gruzelier et al., 1999 (47)	RMT—word memory	RMT—face memory
Halari et al., 2004 (51)	WMS-R—verbal memory logical memory-immediate and delayed recall HVLT—recognition BSRT—total recall, long- & short- term retrieval, total long-term storage, total consistent long- term retrieval, total random long-term retrieval	WMS-R—spatial-memory BVRT—number correct & number of errors
Hoff et al., 1998 (25)	Boston Naming Test Controlled Oral Word Association Test WMS-R—verbal memory-logical memory delay, verbal memory-logical memory A+B, associated learning CVLT—trial 5 BVRT—number of correct BVRT—number of errors	WMS-R—visual reproduction-immediate-delayed
Lewine et al., 1997 (28)	WMS-R—verbal logical memory-delayed WMS-R—verbal logical memory-immediate	WMS-R—spatial memory-visual reproduction-delayed WMS-R—spatial memory-visual reproduction-immediate
Ragland et al., 1999 (52)	WMS-R—verbal memory (logical memory passage-immediate & delayed) CVLT—learning trial 1–5	WMS-R—spatial memory-design reproduction-immediate & delayed
Sota and Heinrichs, 2003 (53)	CVLT— LDFR raw	—

CVLT=California Verbal Learning Test (67); WMS-R=Wechsler Memory Scale-Revised (68); WAIS-R=Wechsler Adult Intelligence Scale-Revised (69); RMT=Recognition Memory Test (70); HVLT=Hopkin Verbal Learning Test (71); BSRT=Buschke Selective Reminding Test (72, 73); BVRT=Benton Visual Retention Test (74); LDFR=long delay free recall

random effect model (see Table 3). By reviewing the standard difference in the means, two studies contributing to the heterogeneity effect were detected and removed from the subsequent analysis (27, 53). The analysis of the remaining eight studies resulted in a nonsignificant, but close to homogeneous effect estimate (effect size [ES]=-0.065; P-value=0.577; confidence interval [CI]=-0.291 to 0.162; Q-value=13.853; P-value=0.054). A fixed effect metaregression analysis also has been performed on the effect estimate to the sample size and revealed that, as the sample size increased, the effect decreased (point estimate slope=-0.003; standard error of the mean [SEM]=0.001; P-value=0.025) supporting the overall nonsignificant effect (see Figure 1).

Meta-analytic evaluation based on eight studies of the nonverbal episodic memory has yielded a significant and nonheterogeneous effect estimate (ES=0.244; P-value=0.005; CI=0.073 to 0.415), revealing that male patients suffering from schizophrenia performed better than female patients. The fixed effect metaregression analysis showed a nonsignificant trend that, as the sample size increased, the effect estimate also increased (slope=0.002; SEM=0.001; P-value=0.229) (see Figure 2).

To keep the weight of the episodic memory subdomains equal in assessment of the global effect estimate, we removed the studies by Fiszdon and colleagues (27) and by Sota and Heinrichs (53), as they reported only results of the verbal memory function. (Incidentally, these were also the studies that contributed to the heterogeneous effect of the verbal memory meta-analysis.) We have pooled the verbal and nonverbal memory results from each study to provide a composite effect estimate per study using CMA (see Table 4). The effect estimate using a random effect model was nonsignificant and homogeneous (see Table 3).

Post Hoc Analysis

Additional analyses taking into account male to female ratio, age of illness onset and patients' IQ have been performed to discover whether these factors might have contributed significantly to the obtained effects. Thus, for the nonverbal episodic memory, a fixed effect regression

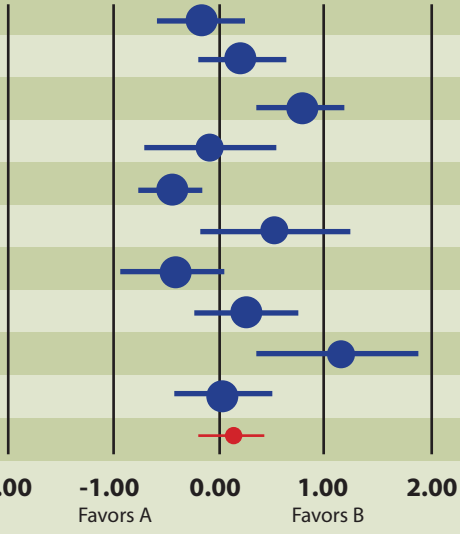
Table 3 Effect Estimates of Gender Differences in Long-Term Memory (LTM) Categories

LTM	Number of Studies	N	ES (Hedges's g)	95% CI	P-Value	Q-Value
Verbal	10	833	0.136	-0.170 to 0.441	0.383	38.028*
Nonverbal	8	699	0.244	0.073 to 0.415	0.005†	8.213
Global	8	699	0.055	-0.083 to 0.193	0.434	4.458

ES=effect size; CI=confidence interval
*heterogeneous
†significant

Figure 1 Blobbogram of the Verbal (V) Memory (N=10)

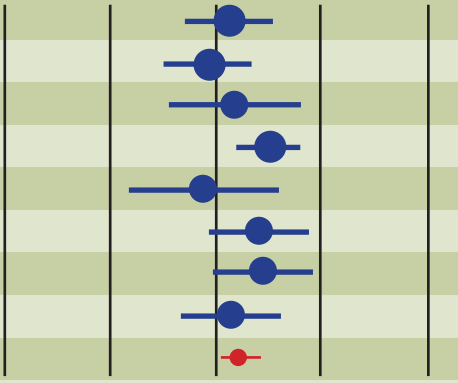
Group by Category	Study	Hedges's g	P-Value	Lower Limit	Upper Limit
V	Gruzelier et al.	-0.195	0.337	-0.592	0.203
V	Hoff et al.	0.141	0.456	-0.229	0.510
V	Sota/Heinrichs	0.804	0.000	0.391	1.218
V	Halari et al.	-0.081	0.803	-0.714	0.552
V	Lewine et al.	-0.449	0.004	-0.755	-0.143
V	Goldstein et al.	0.536	0.135	-0.166	1.237
V	Goldberg et al.	-0.415	0.115	-0.932	0.102
V	Albus et al.	0.259	0.293	-0.224	0.741
V	Fiszdon et al.	1.166	0.004	0.369	1.964
V	Ragland et al.	0.031	0.893	-0.426	0.489
V		0.136	0.383	-0.170	0.441



Random Effect Model

Figure 2 Blobbogram of the Nonverbal (NV) Memory (N=8)

Group by Category	Study	Statistics for Each Study				Hedges's g and 95% CI
		Hedges's g	P-Value	Lower Limit	Upper Limit	
NV	Gruzelier et al.	0.172	0.397	-0.225	0.569	
NV	Hoff et al.	-0.052	0.782	-0.421	0.317	
NV	Halari et al.	0.200	0.536	-0.434	0.834	
NV	Lewine et al.	0.522	0.001	0.214	0.829	
NV	Goldstein et al.	-0.117	0.740	-0.806	0.573	
NV	Goldberg et al.	0.412	0.118	-0.105	0.928	
NV	Albus et al.	0.451	0.069	-0.036	0.937	
NV	Ragland et al.	0.112	0.632	-0.346	0.569	
NV		0.244	0.005	0.073	0.415	



Random Effect Model

analysis considering male to female ratio as a moderating variable was nonsignificant (p-value=0.887). With respect to the illness onset, we were limited to only five studies that reported the data for men and women separately. Thus, the scatter plot of the fixed effect regression analysis of the age of schizophrenia onset for males showed that, as the age of onset increased, the effect estimate also increased; yet, the effect was nonsignificant (p-value=0.51). In contrast, for females the opposite was true: as the age of onset increased, the effect estimate decreased, but again it was nonsignificant (p-value=0.416). The same studies were analyzed for the effect of male and female IQ separately, but the results were nonsignificant (p-value=0.99 and p-value=0.76, respectively).

The analysis of the verbal episodic memory considering possible moderating factors resulted in a nonsignificant effect in terms of male to female ratio (p-value=0.58). Six studies reported the age of illness onset and the IQ for male and female patients separately. While the fixed effect regression analysis of the women's data showed a nonsignificant effect of the age of illness onset, the effect was significant for men (point estimate of the slope=-0.0878; p-value=0.040); as the age of schizophrenia onset increased, the effect estimate decreased. The final metaregression analysis revealed nonsignificant effects for both male IQ (p-value=0.91) and female IQ (p-value=0.84).

Discussion

The main finding of the present preliminary analysis is the lack of sex differences in the verbal memory and a signif-

Table 4 Aggregate of Verbal and Nonverbal Episodic Memory for Eight Studies

Study Authors, Year (Ref #)	ES	P-Value	95% CI
Albus et al., 1997 (29)	0.354	0.043	0.011 to 0.697
Goldberg et al., 1995 (31)	-0.002	0.997	-0.812 to 0.818
Goldstein et al., 1998 (26)	0.206	0.528	-0.433 to 0.845
Gruzelier et al., 1999 (47)	-0.011	0.950	-0.370 to 0.347
Halari et al., 2004 (51)	0.059	0.795	-0.389 to 0.507
Hoff et al., 1998 (25)	0.044	0.741	-0.217 to 0.305
Lewine et al., 1997 (28)	0.036	0.941	-0.915 to 0.987
Ragland et al., 1999 (52)	0.071	0.665	-0.252 to 0.395

ES=effect size; CI=confidence interval

icantly better performance of male relative to female patients in terms of nonverbal memory function. This result deviates slightly from what has been observed in the general population, where the superiority of women on the verbal memory is a much more robust finding (7) than an advantage of men on the nonverbal memory tests (9).

The discrepancy between the present results and the findings in healthy individuals may represent the differential effect that schizophrenic illness has on men and women. For example, it has been well documented that there are significant sex differences in the clinical expression of schizophrenia, with males exhibiting, on average, more pronounced negative symptoms such as social withdrawal, blunted affect, poverty of speech and avolition (56, 57), and females displaying more affective symptoms such as dysphoria, impulsivity, inappropriate affect and more atypical psychotic symptoms (58, 59). These clinical profiles have been related to differential lateralization of brain function. For example, Gruzielier and colleagues (60) have found that patients with activational dominance of the left hemisphere had positive symptoms, while those with activational dominance of the right hemisphere had negative symptoms. In a subsequent study (47), the samples were divided according to gender and the results revealed that, in male patients, most of those with positive symptoms had a greater left hemisphere dominance, while those with negative symptoms had greater right hemisphere pattern; but the opposite was true for females (i.e., those with positive symptoms had a greater right hemisphere dominance, while those with negative symptoms had greater left hemisphere pattern). Because traditionally left hemisphere has been associated with verbal skills and right hemisphere with visuo-spatial abilities, the results obtained by Gruzelier and colleagues imply that stratification of patients into predominant positive and negative symptom subtypes could contribute to better delineation of sex differences in the present analysis. Unfortunately, these data were not available; more studies are needed in this area.

Overall, the issue of sex differences, cognitive function and hemispheric laterality in schizophrenia is quite complex and still underexplored. Collinson et al. (44) have found that changes in brain volume and their relationship to IQ were sexually dimorphic in patients with early-onset schizophrenia. In male patients, reduced left hemisphere volume was correlated with the lower full scale IQ, whereas, in female patients, reduced rightward asymmetry was associated with a selective decrease in verbal IQ. This later result is consistent with the lack of female advantage on verbal episodic memory in the present study.

More recently, Crow et al. (46) imposed additional layers of complexity to the lateralization issue. Based on existing neurodevelopmental theories and empirical findings, they concluded that females are more lateralized anteriorly (prefrontal cortex), while males are more lateralized posteriorly (occipito-parieto-temporal cortex), which leads to better verbal abilities in females and better visuo-spatial function in males. Furthermore, Crow et al. proposed that the transmission of information in the cerebral cortex is predominantly from the areas of greater to lesser size, which results in the direction from left-to-right region posteriorly and from right-to-left anteriorly. This transmission, according to their hypothesis, is disturbed in schizophrenia due to a failure to develop unequivocal lateralization, which may have differential consequences in males and females.

In addition to the potential influence of different symptomatology and hemispheric lateralization, a contributing factor to the present results could be a disturbed level of sex steroid hormones, though this remains highly speculative as we did not have access to any hormonal data in the analyzed samples of patients. Nevertheless, it is worth mentioning that while elevated levels of estrogen have been associated with enhanced performance on verbal memory tasks in healthy women (61, 62), diminished levels of estrogen (hypoestrogenism), either due to antipsychotic-induced hyperprolactinaemia or independently of antipsychotic use, have been observed in numerous studies of schizophrenia patients (48, 49). In an investigation of the relationship of gonadal hormones and cognitive performance, average levels of estrogen over a four-week period have been positively correlated with better verbal and spatial memory and with perceptual-motor speed (25). Interestingly, patients with psychosis, similar to normal women, performed better on spatial tasks when their levels of estrogen were diminished, but did not show an enhanced performance on verbal and motor tasks when their levels of estrogen were augmented (effect observed in healthy women) (63). This could have contributed to the diminished sex difference in verbal episodic memory, but preserved the difference in nonverbal memory function in the present study.

The nonsignificant finding in the verbal memory also might have arisen due to the considerable heterogeneity of patients tested in studies included in the present preliminary meta-analysis (i.e., samples included chronic, long-term, institutionalized inpatients, first-episode patients, and well-functioning outpatients; all with diverse symptomatology, medications, age, education, etc.). We have tried to untangle this heterogeneity by performing additional analyses to reveal potential contribution of male to female ratio, age at illness onset and IQ of men and women patients. However, we were presented with a very small number of studies available for these post hoc analyses, and the only significant finding that had emerged was that the age of illness onset played a significant role only for men in terms of their performance on verbal memory tasks (the earlier the age of schizophrenia onset, the more difficulties in verbal skills they exhibited).

It is worth mentioning here that earlier onset has also been associated with more neural abnormalities (64); therefore, perhaps if we explored only early onset patients the results might be different, but there were not enough studies to fully explore this possibility.

The small number of heterogeneous studies also could have obscured the effects of some other mediating variables. For example, in addition to age, the clinical status could contribute to observable sex differences in cognitive function (e.g., the difference may be more pronounced during the acute phase of schizophrenia). In a similar vein, one of the mediating variables could be treatment with either typical or atypical antipsychotic medications, particularly in light of the evidence that newer antipsychotics elicit significantly less extrapyramidal symptoms than older neuroleptics and appear to be more effective in the treatment of cognitive deficits in schizophrenia (65), though others have not found this effect (66). Moreover, because the studies included in the present meta-analysis explored episodic memory with a wide variety of tests ranging from recognition, through free and cued recall, to immediate versus delayed tasks, we cannot exclude the possibility that the results would be different if we could limit our analysis to a few specific aspects of episodic memory (e.g., the difference between men and women could be most pronounced between strategic versus more automatic processing, or between encoding versus retrieval). Delineation of these and other factors implicated in sex differences in cognitive function in schizophrenia awaits further studies.

Another limitation and obstacle to more thorough interpretations of the present results is the lack of direct comparison with healthy populations but, unfortunately, only a few studies that were included in our preliminary analysis reported the results for the control participants. Despite all of the shortcomings, we decided to report these preliminary findings in order to draw attention to the lack of studies designed specifically to investigate sex differences in schizophrenia and to raise greater awareness of the necessity to consider gender as an important variable in clinical cognitive trials with antipsychotic medications.

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