Gender Differences in Never-Medicated First-Episode Schizophrenia and Medicated Chronic Schizophrenia Patients

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ABSTRACT

Background: Schizophrenia shows gender differences in patients' clinical presentation, neurocognitive impairment, course, and treatment outcome. The aims of this study were to compare gender differences in clinical features and cognitive functioning in first-episode and chronic schizophrenia among Han Chinese inpatients.

Method: We compared gender differences in 262 unmedicated first-episode schizophrenia and 960 chronic schizophrenia inpatients (diagnosed according to *DSM-IV*) to 804 matched healthy controls on sociodemographic characteristics, smoking behavior, and the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). Patients were also rated on the Positive and Negative Syndrome Scale. The study was conducted from December 2006 to May 2008.

Results: Schizophrenia first occurred in both first-episode and chronic schizophrenia patients at a significantly earlier age in male than female patients ($P < .05$ and $P < .001$, respectively). The paranoid subtype of schizophrenia was more common in female patients only in chronic schizophrenia, not first-episode patients. Further, cigarette smoking was more common in male than female patients from both patient groups, and, among men, more chronic schizophrenia patients than controls smoked, while among women, fewer chronic schizophrenia patients than controls smoked. Female chronic schizophrenia patients had more severe positive and general psychopathological symptoms, whereas male patients had more severe negative symptoms. By contrast, first-episode schizophrenia patients showed no gender differences in symptoms and severity. Both first-episode and chronic schizophrenia patients performed worse than controls on most of the cognitive tasks. RBANS attention, delayed memory, and immediate memory were less impaired in female than male chronic schizophrenia patients, and first-episode schizophrenia patients showed no gender differences.

Conclusions: Chronic schizophrenia patients have notable gender differences in the age at onset, smoking, symptom severity, and cognitive function favoring women, but first-episode schizophrenia patients show few gender differences.

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Evidence suggests that gender differences among patients with schizophrenia have included age at onset, symptom severity, treatment response, course of illness, and outcome.[1–3] For example, women with schizophrenia appear to have less severe illness and better global outcomes than men.[4,5] Also, women with schizophrenia are better educated, have held jobs more often, and function better socially than men with schizophrenia.[1] Furthermore, gender differences are apparent in the prevalence of antipsychotic side effects in schizophrenia.[6]

Schizophrenic patients show significant deficits in cognitive performance across a number of domains, including learning, memory, attention, executive functioning, and cognitive processing speed.[7,8] However, there has always been debate about the nature, selectivity, and time of onset of these cognitive dysfunctions in relation to the onset of illness.[9] Consistent with a neurodevelopmental view, some of these deficits seem to predate clinical symptoms and to exacerbate with typical illness onset. However, a probable progression of neuropsychological deficits after the onset of illness has so far been controversial.[10] Additionally, gender differences in these cognitive deficits have produced equivocal findings. Some studies indicate men to be more impaired than women,[11,12] whereas others report the opposite[13,14] or no difference.[15,16] However, robust gender differences have been widely reported favoring men on visuospatial functions and women on verbal abilities in schizophrenia,[17] which is similar to healthy individuals.[18]

Disease characteristics and progression of schizophrenia that differ based on gender can point to areas of altered neurobiology and may provide new treatment approaches. These neurobiological insights may be especially important in first-episode schizophrenic patients in which proper and early initial treatment may significantly affect treatment outcome.[1,19] Few investigations have focused on first-episode and drug-naive schizophrenic patients. Those earlier studies have limited sample sizes and a lack of within-gender matching.[11,20] Unmedicated, first-episode schizophrenia patients appear to be the optimal population to assess gender's effects on this debilitating disease because of minimal confounding factors such as illness duration, medication effects, and medical comorbidities due to illness chronicity.[21] A review of gender differences in cognition for first-episode compared to severely ill schizophrenia concluded that any sex differences in cognitive functioning were due to differences in gender-related symptomatic expressions of the illness.[16] Because the negative symptoms of schizophrenia often covary with cognitive impairment, we examined these 2 domains of psychopathology using multiple regression to examine the association between psychotic symptoms and our cognitive measures.

In this study, we attempted to determine whether gender differences exist in clinical features and cognitive performance between first-episode and chronic schizophrenia patients in a large Chinese

Clinical Points

- Gender differences were compared in 262 unmedicated, first-episode schizophrenia and 960 chronic schizophrenia patients to 804 controls.
- Chronic schizophrenia patients have notable gender differences in age at onset, smoking, symptom severity, and cognitive function, favoring women.
- First-episode schizophrenia patients show few gender differences.

inpatient population. Based on the concept of a progressive pathology of schizophrenic patients, we first hypothesized that a more pronounced gender difference in psychopathological symptoms and cognitive impairments in the chronic compared to the first-episode patient group could be observed. Secondly, we expected that men and women with schizophrenia would generally perform worse on all cognitive tasks compared with the corresponding control subjects; however, women with schizophrenia would perform better on cognitive tasks than men with schizophrenia in chronic patients.

METHOD

Clinical Setting

The study was conducted with inpatients at the Beijing Hui Long Guan Hospital and HeBei Province Veteran Psychiatric Hospital, China. Beijing Hui Long Guan Hospital is located 30 km from central Beijing and serves a catchment area population of 13 million people with more than 1,300 inpatient beds. HeBei Province Rongjun Psychiatric Hospital is located in BaoDing city, about 60 km away from Beijing, and serves about 10 million residents with 700 inpatient beds. These 2 hospitals also have outpatient clinics for follow-up of patients after being discharged from these hospitals. All patients were hospitalized when assessed for this study. The first-episode schizophrenia patients had moderate to severe severity of symptoms (generally with a Clinical Global Impressions [CGI][22] score ≥ 4) and remained inpatients for 8 to 10 weeks, with the study assessments done at about week 2 or 3. The chronic schizophrenia inpatients included about two-thirds of the total schizophrenia populations in these hospitals and had been there for many years. Thus, the clinical settings in this study from China could be considered representative of the situation for acute and chronic inpatient care for schizophrenia in China.

Sampling Procedures

For first-episode schizophrenia patients, we recruited those from consecutive admissions from December 2006 to May 2008 who met the following criteria: (1) an acute episode at study intake that met *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition (*DSM-IV*) criteria for schizophrenia; (2) duration of symptoms not longer than 60 months; (3) no prior treatment with antipsychotic medication; (4) age from 16 to 40 years and Han Chinese ethnicity; (5) current psychotic symptoms of moderate severity or greater, as measured with the CGI (score ≥ 4); and (6) written informed consent provided and ability to take part in neuropsychological assessment. Diagnoses were made for each patient by 2 independent experienced psychiatrists and confirmed by the Structured Clinical Interview for *DSM-IV*.[23] A total of 262 consecutive, drug-naive inpatients with first-episode schizophrenia (male/female = 150/112) were enrolled in the present study.

For the chronic schizophrenic patients, we approached all inpatients using a cross-sectional, naturalistic design. The recruitment criteria included: (1) age 40 to 80 years and Han Chinese ethnicity; (2) confirmed *DSM-IV* diagnosis of schizophrenia; (3) duration of illness of at least 5 years; (4) treatment with stable doses of oral antipsychotic drugs for at least 6 months before entry into the study; and (5) written informed consent provided and ability to take part in neuropsychological assessment. Nine hundred sixty medicated chronic schizophrenic patients (male/female = 784/176) were enrolled. Diagnoses and clinical assessment of these patients were also done using the same methodologies used for the first-episode schizophrenia patients. These patients had schizophrenia for an average (mean ± SD) of 24.4 ± 9.6 years with 10.0 ± 9.5 years of hospitalization. Antipsychotic drug treatment consisted mainly of monotherapy with clozapine (n = 432), risperidone (n = 208), chlorpromazine (n = 69), sulpiride (n = 50), perphenazine (n = 47), quetiapine (n = 42), haloperidol (n = 33), and other typical (n = 42) or other atypical (n = 37) antipsychotics. Mean ± SD antipsychotic dose (in chlorpromazine equivalents) was 462 ± 438 mg/d. The patients had been taking their respective medications for 58 ± 54 months (mean ± SD) at the time of the investigation.

We recruited 804 healthy, age- and gender-matched controls (male/female = 589/215) from the local community. All healthy controls were interviewed by trained investigators, who were supervised by one of the research psychiatrists. Subjects were split according to age into those aged 40 years or older (older control group) and those aged 16–40 years (younger control group). In the present study, the first-episode schizophrenia patients plus healthy controls aged 16–40 years were designated as the younger group, and the chronic schizophrenia patients plus healthy controls aged more than 40 years old as the older group.

A complete medical history and physical examination were obtained from patients and control subjects. Subjects with severe physical diseases were excluded. Neither the schizophrenic patients nor the control subjects suffered from alcohol or illegal drug abuse/dependence. Psychiatric disorders were ruled out among healthy controls by a psychiatric evaluation.

For first-episode schizophrenia patients, 52 of 314 (16.6%) were excluded: not meeting the inclusion criteria (n = 13), acute clinical status that made interviewing and cognitive

assessment difficult or unreliable (n = 24), and inability to comprehend consent procedures or refusal to sign consent forms (n = 15). For the chronic schizophrenia patients, 157 of 1,117 (14.1%) were excluded: not meeting the inclusion criteria (n = 95), inability to comprehend consent procedures or refusal to sign consent forms (n = 39), and clinical status that made interviewing and cognitive assessment difficult or unreliable (n = 23).

The institutional review board of Beijing HuiLongGuan Hospital (Beijing, China) approved this study, and each subject gave written informed consent for participating after the study had been fully explained.

Clinical Measures

Research staff administered a detailed questionnaire that asked for general information, sociodemographic characteristics, smoking behavior, and medical and psychological conditions. Additional information was collected from available medical records and collateral data sources (from family and/or treating clinician).

Four trained psychiatrists completed the Positive and Negative Syndrome Scale (PANSS).[24] After training, repeated assessment showed that these psychiatrists had an interobserver correlation coefficient of 0.84 for the PANSS total score.

The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS, Form A)[25] measured cognitive functioning. We translated the RBANS into Chinese and verified its clinical validity and test-retest reliability among healthy controls and schizophrenic patients.[26]

Statistical Analysis

Group comparisons on demographic and clinical variables used χ^2 or Fisher exact tests for categorical variables and Student *t* tests or analysis of variance (ANOVA) for continuous variables.

Age at onset and clinical symptoms shown on the PANSS were analyzed with a 2 × 2 ANOVA representing the between factors of disease phase (first-episode vs chronic schizophrenia) and gender (male vs female). The RBANS scores required a 3-way 2 × 2 × 2 ANOVA design to include group (patients vs healthy controls) in addition to the disease phase and gender comparisons. For the RBANS comparisons, we also included age and education as covariates in multivariate analyses of covariance for significant gender differences across dependent measures from the RBANS total score and its 5 cognitive domains, with independent predictors being gender, group, and disease phase and the gender-by-disease phase interaction. Effect sizes were also calculated for the 2-way comparisons. Effect sizes represent the mean difference, in standard deviation units, between groups of interest. Multiple regression models were used to quantify the amount of variance in cognitive functioning explained by psychopathological variables, after controlling for several potential confounders, eg, gender, age, years of education, and smoking status. In addition, a survival analysis of age at schizophrenia onset was conducted using cumulative hazard curves. We compared log rank cumulative hazard curves for differences between male and female schizophrenic patients, controlling for age.

SPSS version 15.0 (SPSS, Inc, Chicago, Illinois) was used to do all statistical analysis. Data were presented as mean ± SD. All *P* values were 2-tailed at the significance level of ≤ .05.

RESULTS

Gender Differences in Demographic Characteristics Between First-Episode Schizophrenia Patients and Younger Controls

As shown in Table 1, we found smoking ($P < .001$) as a significant difference between male and female first-episode schizophrenia patients and between male and female younger controls ($P < .001$). However, no significant difference in smoking was observed between male first-episode schizophrenia patients and younger male controls ($P > .05$) or between female first-episode schizophrenia patients and young female controls ($P > .05$).

Compared to their corresponding healthy controls, a higher percentage of female first-episode schizophrenia patients were single or not married ($P < .001$). In addition, compared to their corresponding healthy controls, both male and female first-episode patients had lower body mass indexes (BMIs) (both *P* values < .01).

Gender Differences in Demographic Characteristics Between Chronic Schizophrenia Patients and Older Controls

As shown in Table 1, compared to their corresponding control subjects, more male and female chronic schizophrenia patients were single, had never been married, or were divorced (all *P* values < .001). Furthermore, fewer female than male chronic schizophrenia patients were single or never married (34% for women vs 67% for men; $P < .001$).

Smoking was more common in male than female chronic schizophrenia patients and in male than female older controls (both *P* values < .001). Furthermore, significantly more male chronic schizophrenia patients than older male controls smoked (76% vs 61%); however, fewer female chronic schizophrenia patients than older female controls currently smoked (3% vs 13%) (both *P* values < .01).

In addition, female chronic schizophrenia patients obtained more years of education ($P < .01$), had higher BMIs ($P < .01$), and fewer hospitalization times ($P < .001$) than male chronic schizophrenia patients.

Clinical Features Distinguishing Male From Female First-Episode and Chronic Schizophrenia Patients

Age at schizophrenia onset. Two-way ANOVA showed that there were significant effects of gender ($F_{1,1218} = 13.9$, $P < .001$), disease phase (first-episode schizophrenia vs chronic schizophrenia) ($F_{1,1218} = 7.0$, $P = .008$), and gender × disease phase ($F_{1,1218} = 4.7$, $P = .031$) on age at onset. Within

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Table 1. Demographic and Clinical Data (mean ± SD) in Schizophrenia Patients and Controls Grouped by Gender[a]

	Younger Group[b]				Older Group[b]			
	First-Episode Schizophrenia Patients		Younger Controls		Chronic Schizophrenia Patients		Older Controls	
Clinical Variable	Male (n = 150)	Female (n = 112)	Male (n = 170)	Female (n = 95)	Male (n = 784)	Female (n = 176)	Male (n = 419)	Female (n = 120)
Age, mean ± SD, y	26.3 ± 8.6	27.4 ± 9.4	26.4 ± 7.5	27.4 ± 8.0	47.6 ± 9.8	48.8 ± 12.3	47.9 ± 9.4	49.3 ± 6.8
Education, mean ± SD, y	9.3 ± 3.6	9.1 ± 4.0	9.2 ± 10.7	9.9 ± 3.1	8.9 ± 5.2[c]	11.1 ± 10.0[c]	7.2 ± 5.5[c]	8.9 ± 4.7[c]
BMI, mean ± SD, kg/m^2	21.5 ± 3.2[d]	21.1 ± 3.6[d]	23.4 ± 3.8	23.5 ± 3.9	24.3 ± 3.9[c]	25.5 ± 4.6[c]	25.4 ± 3.7	25.6 ± 4.2
Marital status, n (%)[e]								
Single	98 (68)	67 (60)	108 (64)	25 (27)	520 (67)	59 (34)	35 (8)	3 (3)
Married	40 (28)	41 (37)	61 (36)	67 (72)	125 (16)	63 (36)	357 (86)	113 (94)
Divorced	7 (5)	3 (3)	1 (1)	1 (1)	131 (17)	47 (27)	17 (4)	4 (3)
Deceased	0 (0)	0 (0)	0 (0)	0 (0)	5 (1)	6 (3)	8 (2)	0 (0)
Cigarette smoking, n (%)[f]								
Current smoking	72 (49)	5 (5)	66 (39)	9 (10)	588 (76)	5 (3)	254 (61)	15 (13)
Former smoking	8 (6)	0 (0)	10 (6)	0 (0)	30 (4)	4 (2)	58 (14)	2 (2)
Never smoking	66 (45)	103 (95)	94 (55)	84 (90)	158 (20)	162 (95)	105 (25)	103 (86)

[a]Data are missing for some variables, because not all of the subjects had demographic and clinical data.
[b]Subjects aged 16–40 years were designated as the younger group and those aged more than 40 years as the older group.
[c]There was a significant difference between male and female pairs in each group, all *P* values < .01.
[d]Compared to their corresponding healthy controls, both male and female first-episode patients had lower BMIs (both *P* values < .01).
[e]There was a significant difference in marriage between male and female chronic schizophrenia patients (*P* < .001). Fewer female than male chronic schizophrenia patients were single or never married (*P* < .001). Compared to their corresponding control groups, more male and female chronic schizophrenia patients were single, had never been married, or were divorced (all *P* values < .001), and a higher percentage of female first-episode schizophrenia patients were single or not married (*P* < .001).
[f]Male subjects smoked more cigarettes than female subjects in both patient and healthy control groups (all *P* values < .001). Further, significantly more male chronic schizophrenia patients than older male controls smoked (76% vs 61%); however, fewer female chronic schizophrenia patients than older female controls currently smoked (3% vs 13%) (both *P* values < .01).
Abbreviation: BMI = body mass index.

the first-episode and chronic schizophrenia groups, female patients acquired schizophrenia at a later age compared to male patients (*P* < .05 and *P* < .001, respectively) (Table 2). The cumulative hazard curves for men and women were significantly different both in first-episode schizophrenia patients (log rank χ^2_1=4.01, *P* < .05) and in chronic schizophrenia patients (log rank χ^2_1=34.9, *P* < .001).

Psychopathology. Two-way ANOVA showed that there were significant effects of gender on PANSS positive ($F_{1,1205}$ = 20.6, *P* < .001), negative ($F_{1,1205}$ = 11.6, *P* < .001) and general psychopathology ($F_{1,1205}$ = 4.7, *P* < .05) subscores but not the PANSS total score (*P* > .05). Disease phase (first-episode schizophrenia vs chronic schizophrenia) showed significant effects on PANSS total and all subscale scores (all *P* values < .001). The gender × disease phase interactions showed significant effects on PANSS negative and general psychopathology scores (both *P* values < .05) (Table 2). Furthermore, Table 2 shows that the first-episode schizophrenia group had no gender differences in psychological symptoms (all *P* values > .05). The male chronic schizophrenia patients had significantly lower scores than the female chronic schizophrenia patients on the positive and general psychopathology subscales of the PANSS (both *P* values < .01), whereas the female chronic schizophrenia patients had significantly lower scores than the male chronic schizophrenia patients on the negative subscales of the PANSS (*P* < .01). However, the PANSS total scores were not significantly different between chronic schizophrenia male and female patients (*P* > .05).

In addition, both male and female chronic schizophrenia patients had significantly lower scores than first-episode schizophrenia patients on the PANSS total score, positive symptom subscale, and general psychopathology subscale (all *P* values < .001), but chronic schizophrenia patients had higher scores on the negative symptom subscale (both *P* values < .01).

Schizophrenia subtypes. The chronic schizophrenia, but not the first-episode schizophrenia, patients included significantly more paranoid subtype patients among female than male patients (*P* < .001), as shown in Table 2.

Antipsychotic medications. The patterns of antipsychotic medications taken by male and female chronic schizophrenia patients did not significantly differ, including the proportion receiving typical vs atypical antipsychotic drugs, the mean daily dose (in chlorpromazine equivalents), duration of current antipsychotic use, and the proportion receiving antiparkinsonian drugs (all *P* values > .05).

Cognitive Functioning in First-Episode and Chronic Schizophrenia Patients Grouped by Gender: Case-Control Comparison

Total and index RBANS scores of 214 first-episode schizophrenia patients (male/female = 125/89), 560 chronic schizophrenia patients (male/female = 484/76), 132 younger controls (male/female = 69/63), and 267 older controls (male/female = 217/50) are shown in Table 3. Multivariate analysis of covariance revealed statistically significant differences between schizophrenic patients and controls for all

Table 2. Clinical Data in First-Episode and Chronic Schizophrenia Patients Grouped by Gender[a]

Clinical Variable	First-Episode Schizophrenia patients		Chronic Schizophrenia Patients		Gender		Disease Phase		Gender × Disease Phase	
	Male (n = 150)	Female (n = 112)	Male (n = 784)	Female (n = 176)	*F*	*P* Value	*F*	*P* Value	*F*	*P* Value
Age at onset, mean ± SD, y[b]	25.3 ± 8.5	26.4 ± 10.4	23.1 ± 8.5	25.7 ± 8.2	13.9	< .001	7.0	.008	4.7	.031
Schizophrenia subtypes, n (%)[c]										
Disorganized	4 (2.7)	3 (2.7)	70 (9.1)	4 (2.3)						
Paranoid	72 (48.0)	67 (59.8)	232 (30.1)	76 (44.4)						
Undifferentiated	66 (44.0)	35 (31.3)	34 (4.4)	9 (5.3)						
Residual	8 (5.3)	7 (6.3)	436 (56.5)	82 (48.0)						
PANSS score, mean ± SD										
Positive symptom subscale	20.9 ± 6.5	22.1 ± 6.2	11.2 ± 4.9	13.7 ± 6.7[d]	20.6	< .001	455.6	< .001	1.7	.19
Negative symptom subscale	19.3 ± 7.6	18.4 ± 6.2	22.9 ± 8.6	19.3 ± 8.9[d]	11.6	< .001	11.3	< .001	4.5	.034
General psychopathology subscale	35.3 ± 9.7	35.2 ± 9.4	24.5 ± 6.6	27.0 ± 7.7[d]	4.7	.030	268.5	< .001	4.6	.032
Total score	75.6 ± 17.7	75.4 ± 16.2	58.7 ± 16.5	60.0 ± 18.6	0.4	.56	152.1	< .001	0.2	.66
No. of hospitalizations, mean ± SD	NA	NA	4.2 ± 2.8	3.3 ± 2.5[d]	10.9	< .001				
Antipsychotic types, n										
Atypical	NA	NA	610	148						
Typical	NA	NA	174	28						
Antipsychotic dose (chlorpromazine equivalents), mean ± SD, mg/d	NA	NA	443 ± 402	507 ± 482						
Duration of current drug treatment, mean ± SD, mo	NA	NA	39.8 ± 47.6	34.9 ± 61.3						
Anticholinergic drugs, yes/no, n/n	NA	NA	230/542	48/123						

[a]Data are missing for some variables, because not all of the subjects had demographic and clinical data.
[b]Within the first-episode and chronic schizophrenia groups, female patients acquired schizophrenia at a later age compared to male patients ($P < .05$ and $P < .001$, respectively).
[c]χ^2 test showed significantly more paranoid subtype chronic schizophrenia in female than male patients ($P < .001$), but χ^2 test showed no significant differences in schizophrenia subtypes among male and female first-episode schizophrenia patients ($P > .05$).
[d]Indicates comparison between male and female chronic schizophrenia patients in each group; $P < .01$. However, the first-episode schizophrenia group had no gender differences in psychological symptoms (all *P* values > .05).
Abbreviations: NA = not applicable, PANSS = Positive and Negative Syndrome Scale.

Table 3. Total and Index Scores on the Repeatable Battery for the Assessment of Neuropsychological Status (mean ± SD) for Men and Women With First-Episode and Chronic Schizophrenia

Clinical Variable	Younger Group[a]				Older Group[a]				Diagnosis		Gender		Gender × Diagnosis	
	First-Episode Schizophrenia Patients		Younger Controls		Chronic Schizophrenia Patients		Older Controls							
	Male (n = 125)	Female (n = 89)	Male (n = 69)	Female (n = 63)	Male (n = 484)	Female[b] (n = 76)	Male (n = 217)	Female (n = 50)	*F*[c]	*P*	*F*[c]	*P*	*F*[c]	*P*
Immediate memory	67.6 ± 15.4	69.5 ± 17.6	79.6 ± 12.8	78.4 ± 16.6	58.7 ± 16.0	68.1 ± 20.4***	73.0 ± 18.6	74.9 ± 18.6	136.1	< .001	6.6	.01	2.7	.16
Attention	76.8 ± 18.6	81.8 ± 19.2	94.7 ± 10.7	93.2 ± 21.6	72.4 ± 17.3	83.5 ± 16.3***	86.2 ± 18.1	83.9 ± 20.5	137.5	< .001	4.4	.036	8.3	.004
Language	79.4 ± 15.7	76.9 ± 19.5	96.8 ± 12.1	95.7 ± 15.5	83.1 ± 14.3	86.6 ± 15.9	94.4 ± 11.3	92.5 ± 13.6	215.0	< .001	0.9	.34	0.1	.71
Visuospatial/ construction	80.9 ± 16.3	79.4 ± 17.8	82.4 ± 16.2	79.0 ± 15.1	79.7 ± 18.7	87.2 ± 18.9*	80.8 ± 15.4	78.6 ± 15.5	0.2	.65	0.1	.73	2.0	.16
Delayed memory	71.9 ± 18.9	74.3 ± 20.8	87.4 ± 11.2	85.1 ± 15.6	66.7 ± 19.2	77.9 ± 20.8***	86.5 ± 15.8	86.5 ± 15.6	163.4	< .001	5.1	.024	6.1	.014
Total	69.3 ± 13.7	70.9 ± 17.2	84.4 ± 12.1	82.0 ± 15.0	65.5 ± 14.9	75.6 ± 17.0***	79.5 ± 14.4	78.6 ± 16.1	181.4	< .001	3.0	.08	6.9	.009

[a]Subjects aged 16–40 years were designated as the younger group and those aged more than 40 years as the older group.
[b]Indicates comparison between male and female pairs in each group: *$P < .05$; ***$P < .001$.
[c]*F* value was adjusted for age, education, and smoking due to their significant differences among groups.

cognitive domains ($F_{1,1163} = 421.1$, $P < .0001$). Furthermore, diagnosis (patient vs control) differences were significant for the RBANS total scores and all index scores (all *P* values < .001), except for the RBANS visuospatial/constructional index ($P = .65$) (Table 3). Pairwise post hoc comparisons showed significant differences in the RBANS total score and all index scores (all *P* values < .001), except the RBANS visuospatial/constructional index ($P > .05$) between the younger first-episode schizophrenia patients and younger controls (all *P* values < .0001), with effect sizes ranging from 0.67 to 1.13, and between the older chronic schizophrenia patients and older controls (all *P* values < .0001), with effect sizes ranging from 0.57 to 1.03.

Multivariate analysis of covariance also revealed overall main effects for gender in RBANS immediate memory ($F_{1,1169} = 6.6$, $P = .01$), delayed memory ($F_{1,1169} = 5.1$, $P = .024$), and attention ($F_{1,1169} = 4.4$, $P = .036$) domains. Women performed better than men on these domains. Further analysis showed gender × diagnosis interaction effects on attention ($F = 8.3$, $P = .004$). In order to decompose these two 2-way interactions, we examined patients and controls as well as men and women separately in the younger and older populations.

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Male chronic schizophrenia patients performed worse than female chronic schizophrenia patients on attention ($P < .001$) and RBANS total score ($P < .001$). Furthermore, male chronic schizophrenia patients performed worse than female chronic schizophrenia patients on immediate memory ($P < .001$) and delayed memory ($P < .001$). However, the men and women showed no significant differences in the RBANS total scores or any of the index scores for younger and older healthy controls (all P values $> .05$), or in younger first-episode schizophrenia patients (all P values $> .05$). These results suggested that male chronic schizophrenia patients may have suffered more cognitive impairments than female chronic schizophrenia patients.

Associations of Cognitive Impairment With Clinical Variables

Since we found a gender difference on cognitive impairment in chronic schizophrenia but not first-episode schizophrenia patients, the associations of cognitive impairment with clinical psychopathological variables were examined only in chronic schizophrenia patients. Using multivariate regression analysis, the following variables were independently associated with the RBANS total score: gender ($\beta = 0.14$, $t = 3.65$, $P < .001$), education ($\beta = 0.14$, $t = 3.92$, $P < .001$), PANSS negative symptom score ($\beta = -0.41$, $t = -9.89$, $P < .001$), and PANSS total score ($\beta = -0.77$, $t = -9.89$, $P < .001$). These factors together predicted 22% of the variance of the RBANS total score.

Further, data for the women and men with schizophrenia were analyzed separately to assess gender differences in clinical characteristics associated with cognitive impairment. We hypothesized that the clinical predicators for cognitive function were different in the male and female chronic schizophrenia patients. In male chronic schizophrenia patients, multivariate regression analyses showed the following variables were independently associated with the RBANS total score: PANSS negative symptom score ($\beta = -0.29$, $t = -4.7$, $P < .001$), years of education ($\beta = 0.25$, $t = 4.2$, $P < .001$) and smoking ($\beta = -0.13$, $t = -0.27$, $P < .05$). In female chronic schizophrenia patients, the following variables were independently associated with the RBANS total score: the PANSS negative symptom score ($\beta = -0.38$, $t = -3.6$, $P < .001$) and age ($\beta = -0.24$, $t = -2.4$, $P < .05$).

DISCUSSION

To our knowledge, this is the largest study to date assessing gender differences in schizophrenia in both unmedicated first-episode and chronic schizophrenia patients. A number of important conclusions may be drawn from the data. (1) Male patients were younger when they experienced their first schizophrenic episode compared to female first-episode or chronic schizophrenia patients, which is consistent with previous studies.[27–30] (2) More male patients smoked than female patients. Furthermore, more chronic schizophrenia male patients smoked than controls, and the opposite was true for women. (3) Both first-episode and chronic schizophrenia male patients were more likely than male controls to be single or never married. (4) PANSS scores showed that positive symptoms and general psychopathology were more severe in female (vs male) patients, whereas negative symptoms were more severe in male chronic schizophrenia patients; however, no gender difference in PANSS scores was observed in first-episode schizophrenia patients. (5) First-episode and chronic schizophrenia patients performed worse on cognitive tests compared to controls. More specifically, male chronic schizophrenia patients had significantly worse performance across several domains of cognitive functioning than did female chronic schizophrenia patients, but first-episode schizophrenia patients showed no significant gender differences on cognition.

Age at Onset of Illness

Consistent with numerous studies assessing various ethnic populations, we found an earlier age at onset among men compared to women with schizophrenia in both first-episode and chronic schizophrenia patients.[1–3] However, some studies found no gender differences in age at onset of schizophrenia.[20,31] One study even showed a female preponderance of early onset.[32] These conflicting results may relate to differences in the definition of the age at onset; cultural, traditional, or psychological factors; family history; genetic or biological factors; sample size and representation (community vs outpatients vs inpatients); different stages of disease progression (first episode vs chronic); or different illness courses of patients.

Subtypes and Psychopathology

We found no gender differences in subtypes of schizophrenia and psychopathology in first-episode schizophrenia patients, but strong gender differences in both subtypes and psychopathology in chronic schizophrenia patients. This suggests that the course or evolution of schizophrenia may be different between men and women. Indeed, differences apparent in chronic schizophrenia patients are consistent with many studies noting that negative symptoms occur more often in men than women.[20,31,33] Our study also confirms 2 recent studies reporting that female chronic schizophrenia[5] and first-episode schizophrenia[20] patients exhibited significantly more positive symptomatology.

Our data also confirm other studies showing that male compared to female chronic schizophrenia patients are more susceptible to developing negative symptoms after long-term treatment with antipsychotic drugs.[31,34] In contrast to negative symptoms, chronic schizophrenia female patients in our study exhibited greater positive symptoms of schizophrenia compared to chronic schizophrenia male patients, which is also supported by previous studies.[5,20] Within chronic schizophrenia patients, we found more women than men with the paranoid subtype, consistent with women's higher levels of positive symptoms, such as hallucinations and delusions. The greater frequency of the residual type in men than

women is consistent with the men's higher levels of negative symptoms, such as anhedonia, asociality, or affective flattening.

Smoking

Traditionally, substance abuse has been much less common in Chinese women than men, and we found a similar difference in smoking between gender and among first-episode and chronic schizophrenia patients.[5] First-episode schizophrenia female patients smoked less than first-episode male patients (5% vs 49%), but these rates of smoking were not different from controls (both P values > .05), suggesting that acute psychosis may not affect smoking. Similarly, smoking among chronic schizophrenia patients was less common among women than men (3% vs 76%). However, women with chronic schizophrenia had a much lower likelihood of smoking compared to controls (P < .001). In contrast, men with chronic schizophrenia had a much higher likelihood of smoking compared to controls. Similarly, Tang et al[5] found in a Chinese chronic schizophrenia population that 52% of the male patients smoked, whereas only 4.5% of female patients smoked. Taken together, these findings suggest that as schizophrenia becomes chronic, smoking increases among men, but smoking may remain unchanged or even decrease among women.

Numerous studies have reported that patients with chronic schizophrenia have a higher prevalence of smoking than the general population and other severely mentally ill patients.[34,35] Many Western studies also have shown that although women with schizophrenia smoked less frequently than their male counterparts, the prevalence of current smoking in female schizophrenia patients was much higher that the general population.[35] The reasons for this marked difference in smoking between Western and Chinese chronic schizophrenia women are unknown. Cultural differences may account for the very low general population rates of smoking among female Chinese, which ranges from 5%–9%, and lower rates seen in our chronic schizophrenia female patient population.[36] Because smoking is frowned upon, fewer Chinese women smoke, thus it may be difficult to establish an association between schizophrenia and smoking among women.[34]

Social Functioning

Women are more likely to function better socially than men during the prodromal as well as psychotic phase of schizophrenia.[37] Marital status is one of the strongest indicators of an individual's social functioning. We found a greater percentage of male than female chronic schizophrenia patients were either single or never married. However, divorce was more likely in female than male chronic schizophrenia patients, but this appeared to reflect the greater rate of marriage among female than male chronic schizophrenia patients. These associations are consistent with previous reports.[38] However, in our present study, there was no significant difference in marriage between male and female first-episode schizophrenia patients, suggesting that female patients may show better social functioning over disease progression.

Cognitive Functioning

Consistent with previous studies, we identified broad cognitive impairments with the most notable difficulties in memory, attention, and language among both first-episode and chronic schizophrenia patients.[7,39–41] While the older control group scored lower than the younger control group on the RBANS attention index, immediate memory index, and RBANS total score (all P values < .05) due to aging, the extent of reductions in the RBANS attention, immediate memory index, and total score were significantly greater between chronic and first-episode schizophrenia patients than could be accounted for by aging in controls. Moreover, most cognitive impairment persisted even after a significant improvement in positive symptoms and general psychopathology in the chronic schizophrenia patients. Thus, other factors besides aging during the progress of illness may have contributed to cognitive impairments or decline.

Gender differences were most apparent in chronic schizophrenia, but not for first-episode schizophrenia patients or healthy controls. The relatively worse performance across cognitive domains for the male chronic schizophrenia patients is generally consistent with many, but not all previous studies.[42] Female chronic schizophrenia patients displayed better attention and performed better on delayed memory and immediate memory tasks compared to male chronic schizophrenia patients, suggesting that women could be protected from cognitive deterioration related to schizophrenia. However, this protection appears to be against gradual worsening of schizophrenia over time, not the initial impairments from this disease, since drug-naive first-episode schizophrenia patients showed no gender differences in cognitive impairment. This protection from deterioration in women with schizophrenia may also be related to their fewer negative symptoms. Indeed, we found that RBANS total score was negatively correlated with PANSS negative symptom scores in chronic schizophrenia patients (P < .0001). Our multiple regression statistics relating cognitive functioning to psychotic symptoms, education, age, and smoking made several additional points. (1) Only the negative symptoms from the PANSS were associated with the cognitive functioning scales. (2) The degree of associations were modest and similar for men and women with the negative symptoms accounting for about 10% of the variance in cognitive functioning for men and about 15% for women. (3) Men differed in also having education and smoking as significant associations with cognition, while the women did not.

Strengths and Limitations

A major strength of this study is that we compared the largest sample size of male and female unmedicated first-episode schizophrenic cases to date with a comparable cohort of chronically ill schizophrenic patients. In addition,

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the groups were ethnically homogeneous (all Han Chinese), which limited immigration and population stratification bias. Despite these advantages, however, there are innate limitations to this study. For example, the cross-sectional design we used prevented asserting valid conclusions due to the disease process between genders. That is, it was impossible to tell with certainty whether gender differences seen across first-episode and chronic schizophrenia patients are linked to disease progression or to other factors like who presents in clinics at early vs later stages of illness or other cohort effects. A future longitudinal study could quite likely better reveal significant effects due to disease progression. An additional limitation is that our male to female sample ratio between groups was biased toward men, most notably in the chronic schizophrenia group (chronic schizophrenia: 784/176; first-episode schizophrenia: 150/112). The reasons for fewer female subjects among our chronically ill group may be due to a number of factors such as ceasing treatment later in the course of the disease, receiving care via alternate means (family and residential facility), or better treatment response and recovery compared to men. Further investigation directly exploring possible reasons why this gender imbalance occurred in our chronic patients would help clarify this important issue.

Drug names: clozapine (Clozaril, FazaClo, and others), haloperidol (Haldol and others), quetiapine (Seroquel and others), risperidone (Risperdal and others).

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