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Gender differences in correlates of cognition in first-episode psychosis

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ABSTRACT

Studies of gender cognitive differences in schizophrenia have reported mixed results. This study examined cognitive correlates including demographics, symptoms and functioning in men and women in a large sample of first-episode adult-onset psychosis patients. Detailed demographic, clinical and functioning data were collected from 360 first-episode patients upon admission into an early intervention service for psychotic disorders. They were also administered a comprehensive neurocognitive battery. Correlation analyses showed that memory and working memory were more significantly associated with onset age, negative symptoms and side effects in women. Processing speed correlated with antipsychotic dosage in men and side effects in women. Selective attention correlated with reality distortion and negative symptoms in women, and onset age and education in men. Executive function correlated with onset age and reality distortion in women. All cognitive domains significantly correlated with educational level and functioning in both genders. Negative symptoms explained significant variability in cognition in both genders, while reality distortion, side effects and affective symptoms were significant factors that differentiated between genders. Although there are similarities in cognitive deficits, considerable heterogeneity exists in associations of symptoms and cognition in men and women. Results facilitate individualised tailoring of interventions, including cognitive remediation therapy.

1. Introduction

Although lifetime prevalence of schizophrenia is approximately equal in men and women, there are numerous established gender differences, including earlier age of onset observed in males (Häfner et al., 1998), distinct psychopathology, quicker response to treatment and better functioning and prognosis in women (Leung and Chue, 2000). However, consistent sex differences in neurocognitive performance have not emerged despite extensive research (Ochoa et al., 2012). Some studies supported greater neurocognitive impairment in men (Goldstein et al., 1998; Seidman et al., 1997), some in women (Lewine et al., 1996), while others find no difference (Goldberg et al., 1995; Hoff et al., 1998).

Considering the equivocal results of directly comparing neurocognitive performance between genders, it may be informative to examine the issue by looking at the cognitive correlates of schizophrenic symptoms separately in each gender. Indeed, previous studies have mostly regarded gender as a factor to control for (Ayres et al., 2007). It is possible that, besides from sex differences in symptom presentation, men and women express differential relationships between psychopathology and cognition, which has important implications for future clinical treatment and our understanding of the neurobiological basis of schizophrenia. Our aim in the current study is to investigate the sex differences in correlations between functioning, symptoms and neurocognitive performance in first-episode psychosis (FEP).

Since cognitive deficits are shown to be static over the course of illness (Lewandowski et al., 2011) and predict long-term functioning and outcome (Green et al., 2004), they serve as natural targets for treatments in schizophrenia (Wykes et al., 2011). In mixed-gender samples, robust relationships are documented between negative symptoms and impairment in verbal and working memory, processing speed and executive function (Ayres et al., 2007; Bilder et al., 2000; Heydebrand et al., 2004). Modest correlations between neurocognition and disorganisation have been reported, while associations with reality distortion e.g. hallucinations and delusions have been relatively weak and inconsistent (Galderisi et al., 2009; Lucas et al., 2004). Non-linear associations of affective symptoms, processing speed and executive function have also been observed (Kravariti et al., 2012). The influence

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of duration of untreated psychosis (DUP) on cognition is debated with studies reporting conflicting results, possibly due to varying methodologies and definitions (Chang et al., 2013; Goldberg et al., 2009; Lutgens et al., 2014).

In this study, we examined whether the relationship between symptoms and neurocognitive function differed in males and females with adult-onset FEP. Data from this study are taken from the Jockey Club Early Psychosis (JCEP) Project in Hong Kong and constitute a large representative sample of adult-onset FEP patients assessed shortly after onset (Hui et al., 2014). In FEP patients, any effects of prolonged exposure to antipsychotic medication and institutionalisation on cognition are minimised (Harvey and Keefe, 2001)—critical due to the different treatment response of men and women, and the greater probability of men developing chronic schizophrenia. There is also evidence that adult-onset patients, containing a greater preponderance of women, have a different neurocognitive profile compared to the adolescent-onset group (Rajji et al., 2009).

2. Methods

2.1. Participants and study setting

The JCEP Project is a population-based territory-wide study providing specialised early intervention services to adult-onset FEP patients (Hui et al., 2014). Eligible participants (n = 360) from every hospital cluster in the public health system were consecutively recruited into the study from 2009 to 2011.

Participants were Cantonese-speaking Chinese between 26–55 with a diagnosis of psychosis for the first time, defined as having received antipsychotic treatment for no more than 12 months following onset. Written informed consent was obtained from all participants. Exclusion criteria were patients with organic brain conditions, substance-induced psychosis, known history of intellectual disability, or risk of suicidal or violent behaviour. The study was approved by the Institutional Review Boards at each study site, and carried out in accordance with Good Clinical Practice and ethical standards in the Declaration of Helsinki.

2.1. Demographic and clinical characteristics

Demographic characteristics including age, gender, years of education, occupational and marital status were recorded, and information about hospitalisation, type and dose of antipsychotic medication was collected at baseline through face-to-face interviews by trained research staff. Diagnosis was assessed by two experienced psychiatrists based on best-estimate consensus approach in each subject (Leckman et al., 1982) according to DSM-IV criteria (American Psychiatric Association, 2000). All sources of information were taken into account, including the validated Chinese version of the Structured Clinical Interview for DSM-IV (So et al., 2003), medical records and history supplied by informants and JCEP case workers. The study included participants with diagnoses of schizophrenia, schizophreniform psychosis, schizoaffective disorder, brief psychotic disorder, delusional disorder, psychosis not otherwise specified or manic episodes with psychotic features.

Illness onset and presentation were assessed with the Interview for the Retrospective Assessment of Onset of Schizophrenia (IRAOS) (Häfner et al., 1992) using operationalized definitions for age of onset, mode of onset and DUP, defined as the period between the onset of psychotic symptoms and receipt of antipsychotic treatment.

2.2. Clinical and functioning measures

Positive and negative symptoms were rated at baseline by research staff using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987), Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984) and Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1983). Depressive and manic symptoms were assessed with the Calgary Depression Scale (CDS) (Addington et al., 1993) and Young's Mania Rating Scale (YMRS) (Young et al., 1978), respectively. Medication side-effects were assessed with Udvalg for Kliniske Undersøgelser (UKU) (Lingjaerde et al., 1987). Functioning level was measured with the Social and Occupational Functioning Assessment Scale (SOFAS) which has scores ranging from 1 to 100, with higher scores indicating better social and occupational functioning (Goldman et al., 1992). There was satisfactory inter-rater reliability among research staff responsible for direct interviews and data collection (Intra-Class Correlation coefficients were 0.93 for PANSS, 0.81 for SAPS and 0.75 for SANS).

2.3. Neurocognitive assessments

Participants were administered a comprehensive battery of neurocognitive tests at baseline assessing six neurocognitive domains: (a) working memory was assessed with Backward Digit Span and Arithmetic subtests from Wechsler Adult Intelligence Scale – Revised (Wechsler, 1981); (b) verbal and visual short-term memory was estimated with Logical Memory (WAIS-R) and Visual Patterns Test (Della Sala et al., 1999); (c) speed of processing was measured with Digit Symbol (WAIS-R); (d) general attention was measured with Forward Digit Span (WAIS-R); (e) selective attention was assessed with the card version of Stroop Word-Colour Test (Golden, 1978); and (f) executive function was measured with the Modified Wisconsin Card Sorting Test (Nelson, 1976).

2.4. Statistical analysis

A composite measure of working memory was produced by standardising the summed raw scores of Backward Digit Span and Arithmetic. Likewise, a standardised memory score was calculated from performance in Logical Memory (immediate and delayed recall) and Visual Patterns Test (number correct). Raw scores from individual neurocognitive tests were transformed into standardised z-scores for remaining four domains: general attention (Forward Digit Span), selective attention (Stroop interference condition speed and accuracy), speed of processing (Digit Symbol) and executive function (WCST total correct, perseverative and non-perseverative errors). Shapiro-Wilks normality test indicated that the six cognitive domains, age of onset, years of education and functioning score were non-normally distributed ($p < 0.05$); however, considering the large sample size (n = 360) and high W statistics, the distributions are assumed to be near-normal and parametric tests were used. Stroop interference accuracy, WCST number of correct responses and perseverative errors had W statistics < 0.85 and inspection of their histograms suggested non-normal distributions; DUP was also significantly skewed, thus non-parametric tests were used in later analysis.

To reduce the number of comparisons in subsequent analyses, a Principal Component Analysis (PCA) was performed on the section total scores of PANSS, SAPS, SANS, UKU, and total scores of YMRS and CDS with a Varimax rotation method, and all factors with eigenvalues greater than 1 were extracted resulting in a 5-factor solution for symptom dimensions. Independent sample t-tests and Wilcoxon rank tests were used to compare demographic, clinical and functional characteristics, symptom dimensions and cognitive domains of men and women. Separate Pearson and Spearman bivariate correlation analyses were performed to investigate gender-specific associations. Lastly, variables from significant correlations were analysed using linear regression with cognitive domains as dependent variables, symptom dimensions as independent variables and other factors such as age of onset and education as covariates. All analyses were carried out with the SPSS statistical software package (version 24.0).

Table 1
Comparison of demographic and clinical characteristics in men and women.

Demographics	Men (n = 157)	Women (n = 203)	$P^{\#}$
Age of onset, mean (SD)	35.2 (8.7)	37.6 (8.6)	**.008**
Years of education, mean (SD)	11.2 (3.8)	10.3 (3.9)	**.022**
Married, *n* (%)	47 (29.9)	77 (37.9)	NS
Working/studying at entry, *n* (%)	71 (45.2)	109 (53.7)	NS
Clinical characteristics			
SOFAS, mean (SD)	58.2 (14.4)	60.2 (12.7)	NS
DUP, days, median (IQR)	104.0 (19.0–646.5)	91.0 (21.0–303.0)	NS
Diagnosis, *n* (%)			
Schizophrenia	75 (48.1)	82 (40.2)	NS
Schizophreniform psychosis	20 (12.8)	40 (19.6)	NS
Schizoaffective disorder	2 (1.3)	2 (1.0)	NS
Brief psychotic disorder	16 (10.3)	26 (12.7)	NS
Delusional disorder	32 (20.5)	40 (19.6)	NS
Manic episodes with psychotic features	1 (0.6)	4 (2.0)	NS
Psychotic disorder not otherwise specified	10 (6.4)	10 (4.9)	NS
Antipsychotic medication type, *n* (%)			
Conventional	36 (23.1)	52 (26)	NS
Atypical	114 (73.1)	141 (69.1)	NS
Conventional and atypical	4 (2.6)	0	NS
No medication	2 (1.3)	10 (4.9)	NS
Antipsychotic medication chlorpromazine equivalent dosage, mg, mean (SD)	169.0 (127.3)	167.3 (156.3)	NS

SD: standard deviation; *n*: number; NS: not significant; IQR: inter-quarter range; SOFAS: social and occupational functioning assessment scale; DUP: duration of untreated psychosis.

[#] *p*-values smaller than 0.05 are bolded.

3. Results

3.1. Demographic and clinical characteristics

There were 360 patients in total (43.6% male, n = 157). The mean age of onset was 36.6 ± 8.7 years, and mean years of education were 10.7 ± 3.9 years. At baseline, 96.7% (n = 348) of the population were on antipsychotic medication. Table 1 compares demographic and clinical data between male and female patients. Men had significantly younger age of onset ($t = -2.7$, $p = 0.008$) and more years of education ($t = 2.3$, $p = 0.02$). No significant differences were found in social and occupational functioning, DUP, diagnosis, or medication type and dosage. All intake assessments were carried out within a mean of 120 days (SD = 99.6) from a first episode of psychosis.

3.2. Factor analysis and neurocognitive performance

The PCA analysis was conducted on 18 section subtotals in PANSS (positive symptoms, negative symptoms), SAPS (hallucinations, delusions, bizarre behaviour, positive formal thought disorder, inappropriate affect), SANS (affective flattening, alogia, avolition-apathy, anhedonia-asociality, attention), UKU (psychic, neurologic, autonomic, others), CDS (sum of all items) and YMRS (sum of all items) with orthogonal rotation (Varimax). The sampling adequacy was sufficient according to the Kaiser-Meyer-Olkin measure (0.72) and Bartlett's test of sphericity ($\chi^2(153) = 2280.8$, $p < 0.001$).

Five factors with eigenvalues >1 were extracted, and together explained 62.2% of the variance. Factors 1, 2 and 4 corresponded to the negative, positive and disorganisation dimensions observed in schizophrenia (Andreasen et al., 1995). Factor 3 represented medication side effects while affective symptoms (mania, depression) loaded onto Factor 5. Factor scores were generated for each patient using regression and adopted in subsequent analyses. Negative and positive symptoms, disorganisation and affective symptoms had significantly non-normal distributions and W statistics were <0.85. Factor loadings of the 5 factors after rotation are shown in Table 2.

Symptom factor scores and neurocognitive performance of male and female patients were compared. Men had significantly more negative symptoms ($t = -2.5$, $p = 0.012$), less medication side effects ($t = -2.6$, $p = 0.009$), and better working memory ($t = -3.7$, $p < 0.001$). No significant gender differences were found in the severity of positive symptoms, disorganisation and affective symptoms, or performance on other neurocognitive tests.

Table 2
Five-factor principal component analysis of clinical rating scores with varimax rotation.[#]

Item	Factor 1 (Negative symptoms)	Factor 2 (Positive symptoms)	Factor 3 (Medication side effects)	Factor 4 (Disorganisation)	Factor 5 (Affective symptoms)
PANSS positive		**.941**			
PANSS negative	**.870**				
SAPS					
Hallucination		**.669**			
Delusion		**.826**			
Bizarre behaviour		.351			
Formal thought disorder		.512		**.630**	
Inappropriate affect				**.785**	
SANS					
Affective flattening	**.816**				
Alogia	**.686**				
Avolition-apathy	**.709**				
Anhedonia-asociality	**.744**				
Attention	.444			.473	
UKU					
Psychic			**.772**		
Neurologic			**.692**		
Autonomic			**.814**		
Others			**.754**		
CDS total			.303		**.600**
YMRS total					**.866**

PANSS: Positive and Negative Syndrome Scale; SAPS: Scale for the Assessment of Positive Symptoms; SANS: Scale for the Assessment of Negative Symptoms; UKU: Udvalg for Kliniske Undersøgelser; CDS: Calgary Depression Scale; YMRS: Young's Mania Rating Scale.

[#] Factor loadings greater than 0.60 are bolded.

Table 3
Correlations between DUP, age at onset, education, functioning and five symptom dimensions in males and females.

Variables	Factor 1 (Negative symptoms)[b]		Factor 2 (Positive symptoms)[b]		Factor 3 (Medication side effects)[a]		Factor 4 (Disorganisation)[b]		Factor 5 (Affective symptoms)[b]	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
DUP[b]	−0.009 (0.916)	0.107 (0.142)	**0.211** ** **(0.009)**	**0.310** ** **(0.000)**	−0.048 (0.560)	0.076 (0.297)	−0.109 (0.182)	−0.025 (0.731)	**0.318** ** **(0.000)**	0.075 (0.303)
Age of onset[a]	0.011 (0.890)	0.136 (0.062)	0.149 (0.069)	0.035 (0.634)	−0.009 (0.913)	0.125 (0.086)	−0.138 (0.092)	−0.085 (0.191)	0.112 (0.173)	0.036 (0.624)
Education[a]	−0.132 (0.108)	−0.083 (0.255)	−0.185* (0.024)	−0.116 (0.109)	−0.184* (0.024)	−0.003 (0.966)	0.115 (0.161)	0.032 (0.662)	−0.080 (0.331)	−0.090 (0.214)
Total chlorpromazine eq. doses[b]	0.108 (0.187)	0.057 (0.435)	0.012 (0.886)	−0.024 (0.738)	0.102 (0.215)	0.108 (0.137)	0.094 (0.252)	0.105 (0.150)	−0.035 (0.671)	0.036 (0.622)
SOFAS[a]	**−0.380** ** **(0.000)**	**−0.446** ** **(0.000)**	**−0.269** ** **(0.001)**	**−0.244** ** **(0.001)**	−0.204* (0.012)	**−0.312** ** **(0.000)**	0.172 (0.036)	0.105 (0.150)	**−0.293** ** **(0.000)**	**−0.283** ** **(0.000)**

DUP: Duration of Untreated Psychosis; SOFAS: Social and Occupational Functioning Assessment Scale; r: Pearson's correlation coefficient for near-normal distributions (a) or Spearman's correlation coefficient for non-normal distributions (b).

* $p < 0.05$ and $q < 0.05$,

** $p < 0.01$ and $q < 0.05$ (bolded)

3.3. Correlates of symptoms, functioning and neurocognition

Due to the exploratory nature of our study and intercorrelation of the symptom and neurocognitive domains, the False Discovery Rate (FDR) method was used to control for multiple comparisons (Benjamini and Hochberg, 1995). Only correlations with both p and q-values < 0.05 were considered significant. Amongst the five symptom dimensions, negative symptoms significantly correlated with affective symptoms only in men ($r_s = 0.31$, $p < 0.001$), and with affective symptoms ($r_s = 0.30$, $p < 0.001$), side effects ($r_s = 0.20$, $p = 0.006$) and disorganisation in women ($r_s = -0.26$, $p < 0.001$). Positive symptoms strongly correlated with disorganisation in both genders ($r_s = -0.43$, $p < 0.001$ in men; $r_s = -0.48$, $p < 0.001$ in women) and additionally with affective symptoms in men ($r_s = 0.22$, $p = 0.008$).

Table 3 compares correlations between DUP, age at onset, education, functioning and five symptom dimensions for men and women. DUP was significantly correlated with the severity of positive symptoms in both sexes, especially in women, and associated with affective symptom severity in men. Social and occupational functioning in both sexes was significantly correlated with all symptom dimensions except disorganisation. The negative correlation between functioning and medication side effects was greater in women.

Correlations between the demographic and clinical variables, symptom dimensions and neurocognitive performance scores of males and females are presented in Table 4. DUP and disorganisation did not significantly correlate with any neurocognitive variables. Age of onset correlated significantly with processing speed and Stroop interference time taken in both sexes, and more strongly with working memory, memory, and executive function in women. As expected, education strongly correlated with all neurocognitive variables except Stroop interference time taken and executive function in women. Total antipsychotic dosage was only significantly associated with processing speed in men. Functioning in women was significantly associated with all neurocognitive measures except WCST non-perseverative errors; it significantly correlated with working memory, processing speed and general attention in men.

Also, negative symptoms were significantly correlated in both sexes with performance on the digit symbol subtest and Stroop interference time taken, two measures measuring processing speed. Memory and working memory are more strongly associated with negative symptoms in women. Positive symptoms showed significant negative correlations with Stroop interference accuracy and executive function, especially perseveration, in women, and a trend of association with general attention in both sexes. Medication side effects significantly correlated with working memory and processing speed in women. Affective symptoms had a significant association with general attention in women, and modest correlations with working memory, general attention and processing speed in men.

3.4. Regression models

Linear regressions for the six neurocognitive measures were performed for both genders using all statistically significant associations ($p < 0.05$ and $q < 0.05$) within DUP, age of onset, years of education, total antipsychotic equivalent dosage, and the five symptom domains. Bonferroni correction for multiple comparisons was used, and significant models after correction are summarised in Table 5. Semi-partial correlations were provided as they are more reliable than beta for estimating the relative importance of each variable. All predictors showed relative independence with $r < 0.5$ and no evidence of co-linearity.

After controlling for confounding factors such as age of onset and education, negative symptoms accounted for significant variance in memory, processing speed and selective attention (time taken) in both genders. Positive symptoms predicted general and selective attention (accuracy), and affective symptoms predicted working memory in men. In women, increased medication side effects were associated with

Table 4

Correlations between demographic and clinical variables, symptom dimensions and neurocognitive performance scores in males and females.

	Neurocognitive performance Working Memory[a]		Memory[a]		Speed of Processing[a]		General Attention DS forward[a]	
	Male	Female	Male	Female	Male	Female	Male	Female
DUP[b]	0.012 (0.881)	−0.024 (0.736)	−0.054 (0.499)	0.005 (0.947)	−0.010 (0.897)	−0.120 (0.090)	−0.006 (0.944)	−0.084 (0.235)
Age of onset[a]	−0.124 (0.121)	−0.293** (0.000)	−0.189* (0.018)	−0.340** (0.000)	−0.440** (0.000)	−0.429** (0.000)	−0.148* (0.036)	−0.132 (0.063)
Education[a]	0.547** (0.000)	0.496** (0.000)	0.479** (0.000)	0.372** (0.000)	0.439** (0.000)	0.455** (0.000)	0.357** (0.000)	0.328** (0.000)
Total chlorpromazine eq. doses[b]	0.008 (0.923)	−0.014 (0.843)	−0.119 (0.139)	−0.094 (0.196)	−0.215** (0.007)	−0.122 (0.092)	−0.015 (0.856)	−0.136 (0.062)
SOFAS[a]	0.212** (0.008)	0.269** (0.000)	0.196* (0.014)	0.222** (0.001)	0.232** (0.004)	0.335** (0.000)	0.212** (0.008)	0.162* (0.022)
Negative symptoms[b]	−0.111 (0.175)	−0.232** (0.001)	−0.184* (0.024)	−0.204** (0.005)	−0.210* (0.010)	−0.316** (0.000)	−0.019 (0.821)	−0.114 (0.120)
Positive symptoms[b]	−0.132 (0.106)	−0.140 (0.053)	−0.045 (0.584)	−0.002 (0.978)	−0.135 (0.102)	−0.106 (0.148)	−0.186* (0.023)	−0.154* (0.035)
Medication side effects[a]	−0.172* (0.036)	−0.200** (0.006)	−0.067 (0.415)	−0.050 (0.495)	−0.100 (0.224)	−0.272** (0.000)	0.030 (0.717)	0.00 (0.999)
Disorganisation[b]	−0.029 (0.725)	0.051 (0.482)	−0.037 (0.657)	0.007 (0.926)	0.063 (0.445)	0.045 (0.535)	0.012 (0.889)	0.084 (0.256)
Affective symptoms[b]	−0.204* (0.012)	−0.125 (0.085)	−0.105 (0.200)	−0.075 (0.302)	−0.174* (0.034)	−0.095 (0.195)	−0.182* (0.026)	−0.198** (0.007)

	Neurocognitive performance Selective Attention Stroop interference (accuracy) [b]		Stroop interference (time) [a]		Executive Function WCST (total correct) [a]		WCST (non-perseverative errors) [a]		WCST (perseverative errors) [b]	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
DUP[b]	0.052 (0.535)	−0.013 (0.855)	−0.078 (0.351)	−0.068 (0.350)	−0.019 (0.824)	−0.086 (0.250)	0.039 (0.653)	−0.081 (0.280)	0.043 (0.622)	0.139 (0.063)
Age of onset[a]	−0.138 (0.099)	−0.144 (0.047)	0.304** (0.000)	0.181* (0.013)	−0.109 (0.210)	−0.215** (0.004)	0.156 (0.072)	0.269** (0.000)	0.112 (0.198)	0.239** (0.001)
Education[a]	0.226** (0.007)	0.303** (0.000)	−0.232** (0.005)	−0.144 (0.048)	0.315** (0.000)	0.149 (0.046)	−0.355** (0.000)	−0.250** (0.001)	−0.418** (0.000)	−0.253** (0.001)
Total chlorpromazine eq. doses[b]	0.011 (0.893)	−0.065 (0.383)	−0.019 (0.819)	0.068 (0.364)	−0.067 (0.444)	−0.105 (0.172)	0.110 (0.211)	0.054 (0.486)	0.104 (0.236)	0.165* (0.031)
SOFAS[a]	−0.021 (0.802)	0.225** (0.002)	−0.150 (0.074)	−0.272** (0.000)	0.106 (0.226)	0.208** (0.005)	−0.024 (0.783)	−0.137 (0.068)	0.014 (0.873)	−0.246** (0.001)
Negative symptoms[b]	−0.177* (0.039)	−0.096 (0.353)	0.278** (0.001)	0.224** (0.003)	−0.182* (0.038)	−0.176* (0.022)	0.159 (0.072)	0.161* (0.036)	0.159 (0.071)	0.171* (0.025)
Positive symptoms[b]	−0.095 (0.271)	−0.224** (0.003)	0.052 (0.544)	0.107 (0.156)	−0.099 (0.261)	−0.158* (0.039)	0.033 (0.712)	.179* (0.019)	0.048 (0.591)	.197** (0.010)
Medication side effects[a]	0.065 (0.447)	0.058 (0.444)	0.026 (0.758)	0.034 (0.657)	0.014 (0.874)	0.097 (0.207)	0.038 (0.665)	0.052 (0.495)	0.014 (0.879)	0.082 (0.284)
Disorganisation[b]	0.089 (0.299)	0.126 (0.092)	−0.016 (0.852)	−0.051 (0.498)	−0.096 (0.279)	0.050 (0.515)	0.028 (0.753)	−0.052 (0.499)	0.066 (0.453)	0.015 (0.843)
Affective symptoms[b]	−0.147 (0.085)	−0.135 (0.072)	−0.002 (0.980)	0.127 (0.091)	−0.077 (0.384)	−0.071 (0.356)	0.069 (0.435)	0.044 (0.569)	0.096 (0.277)	0.097 (0.205)

DUP: Duration of Untreated Psychosis; SOFAS: Social and Occupational Functioning Assessment Scale; DS: Digit Span Task; WCST: Wisconsin Card Sorting Test (Modified); r: Pearson's correlation coefficient for near-normal distributions (a) or Spearman's correlation coefficient for non-normal distributions (b).

* $p < 0.05$ and $q < 0.05$,

** $p < 0.01$ and $q < 0.05$ (bolded)

Table 5
Regression models.

	Age of psychosis onset		Education		Total chlorprom. eq. doses		Negative symptoms		Positive symptoms		Medication side effects		Affective symptoms	
	Part	*p*	Part	*p*	Part	*p*	Part	*p*	Part	*p*	Part	*p*	Part	*p*
Working memory														
Male			0.496	< 0.001									**−0.143**	**0.045**
Female			0.414	< 0.001										
Models are significant: Male [R^2 = 0.332, F(5,138) = 13.247, $p < 0.001$]; female [R^2 = 0.315, F(5,173) = 15.467, $p < 0.001$]														
Memory														
Male			0.401	< 0.001			−0.163	0.023						
Female	**−0.217**	**0.001**	0.266	< 0.001			−0.132	0.044						
Models are significant: Male [R^2 = 0.259, F(3,149) = 17.023, $p < 0.001$]; female [R^2 = 0.212, F(3,189) = 16.655, $p < 0.001$]														
Processing speed														
Male	−0.312	< 0.001	0.268	< 0.001	−0.160	0.019	−0.141	0.039						
Female	−0.265	< 0.001	0.333	< 0.001			−0.146	0.012			**−0.171**	**0.004**		
Models are significant: Male [R^2 = 0.349, F(6,148) = 12.662, $p < 0.001$]; female [R^2 = 0.389, F(6,188) = 19.301, $p < 0.001$]														
General attention														
Male			0.246	0.001					**−0.176**	**.020**				
Female			0.273	< 0.001										
Models are significant: Male [R^2 = 0.192, F(4,148) = 8.557, $p < 0.001$]; female [R^2 = 0.166, F(4,186) = 8.645, $p < 0.001$]														
Selective attention (Stroop colour-word accuracy)														
Male	**−0.189**	**0.018**							**−0.257**	**0.001**				
Female			**0.266**	**< 0.001**									**−0.189**	**0.007**
Models are significant: Male [R^2 = 0.170, F(4,137) = 6.808, $p < 0.001$]; female [R^2 = 0.169, F(4,178) = 8.818, $p < 0.001$]														
Selective attention (Stroop colour-word time taken)														
Male	0.248	0.002					0.214	0.007						
Female	0.194	0.005	**−0.159**	**0.020**			0.300	< 0.001						
Models are significant: Male [R^2 = 0.194, F(4,137) = 8.011, $p < 0.001$]; female [R^2 = 0.213, F(4,177) = 11.704, $p < 0.001$]														
Executive function (WCST total correct)														
Male			**0.240**	**0.004**			−0.183	0.028						
Model is significant: Male [R^2 = 0.151, F(4,129) = 5.561, $p < 0.001$]														
Executive function (WCST non-perseverative errors)														
Male			−0.285	0.001										
Female	**0.205**	**0.005**	−0.148	0.042										
Models are significant: Male [R^2 = 0.152, F(4,129) = 5.595, $p < 0.001$]; female [R^2 = 0.129, F(4,170) = 6.147, $p < 0.001$]														

The variable was used as a predictor in the linear regression for that cognitive domain.
WCST total correct (female) and perseverative errors were omitted because the models were not significant after Bonferroni correction for multiple comparisons. ($p > 0.00357$)

slower processing speed, and more severe affective symptoms were related to poorer selective attention.

4. Discussion

Traditionally, adult-onset psychosis, defined as having an age of onset after 25 years in the current study, is an understudied population compared to early-onset psychosis despite comprising up to a quarter of patients (Howard et al., 2000; Kessler et al., 2005). This study aimed to investigate and characterise any gender differences in psychotic symptoms and cognition a large sample of adult-onset FEP patients in Hong Kong. We found that the relationship between negative symptoms and processing speed, working memory are similar in males and females, while reporting a significant association between positive symptoms, short-term and selective attention in men. Side effects from medication were more severe in women and correlated to impaired working memory and processing speed, while disorganisation did not show any clear relationship with cognition. Lastly, the gender profile of symptoms, cognition and demographics in our sample were broadly consistent with previous research. Results from our study can enable the understanding of the potentially distinct neurocognitive deficits in males and females during the disease process, thereby developing more individualised treatment and rehabilitation plans for patients with adult-onset FEP.

4.1. Gender differences in correlates of cognition

4.1.1. Negative symptoms

Cognitive deficits had been observed in memory, attention, verbal fluency, processing speed and executive functioning in first-episode patients (Ayres et al., 2007; Bilder et al., 2000; Heydebrand et al., 2004). The relationship between negative symptoms and impairment in multiple cognitive domains has been one of the clearest findings in studies of schizophrenia. Although there is speculation of a common aetiology for the two, evidence points toward them being related but dissociable constructs (Harvey et al., 2006). In this study, we found significant association between negative symptoms and processing speed in both genders, with stronger associations with memory and working memory in women. After regression analysis, negative symptoms accounted for a small portion (13–18%) of the variance in memory and processing speed, but a rather greater amount (> 20%) in the Stroop time taken, and did not predict performance in working memory. The high explanatory power of negative symptoms can be attributed to SANS items measuring very similar behavioural aspects as the time taken for Stroop e.g. slowing of speech. Our results largely affirm previous findings, and the lack of significant gender differences in predictors suggest that neurobiological processes underlying negative symptomatology and related cognitive impairments are identical in men and women.

4.1.2. Positive symptoms

There is active debate about the existence and type of cognitive correlates of positive symptoms. Most studies report little to no associations between neurocognitive measures and reality distortion (Dibben et al., 2009; Heydebrand et al., 2004; Ventura et al., 2010), but comparison is often complicated by the different neuropsychological tests used in each. In accordance with our expectations, correlations between positive symptoms and neurocognitive domains were generally weak. Reality distortion in women had stronger associations with selective attention and deficits in executive function, but the relationship was not borne out in subsequent linear analyses, which showed that onset age and education were the only significant factors related to neurocognitive performance.

Interestingly, in our sample positive symptom severity significantly correlated with both general (forward digit span) and selective attention (card Stroop accuracy) in men. An association with poorer forward digit span has been reported previously in a mostly male sample of chronic schizophrenia (Berman et al., 1997). Impaired auditory attention may indicate a serious interference of processing capacity in patients with active psychotic symptoms, such that even low demand tasks are affected (Nieuwenstein et al., 2001). Increased interference in the card Stroop task has also been demonstrated in schizophrenia, reflecting a reduced ability to suppress irrelevant responses and selectively attend when salient distracters are present.

Thus our current findings are broadly consistent with an existing tradition in the schizophrenia research literature of deficits in attentional tasks (Gooding et al., 2006), as well as studies reporting correlations between reality distortion and attentional impairments, usually in chronic populations (Berman et al., 1997; Ventura et al., 2010). Along with evidence from human experimental psychology, our data provide increased support for neuropsychological theories of delusions (Blackwood et al., 2001) hypothesising that subtle deficits in attentional or information processing capability contribute to the formation and maintenance of delusions and hallucinations.

However, our results suggest for the first time that the link between positive symptoms and attention may be modulated by gender. This sex difference may account for the inconsistent findings and small effect sizes in studies to date; it is also possible that the relationship to positive symptoms weaken as chronicity develops and cognitive deficits become more entrenched. Further research focusing specifically on gender differences is needed to elucidate whether positive symptomatology and attentional abnormalities are articulated through different neuromechanisms in men and women.

4.1.3. Affective symptoms and medication side effects

Affective symptoms, encompassing mania and depression, explained significant variance in Stroop accuracy in women and working memory in men. Further analysis of CDS and YMRS scores separately indicates that the manic component is responsible for the significant associations. Studies looking at mania in psychosis have noted cognitive correlates, but the nature of the association remains to be characterised. Kravariti et al. (2012) reported a non-linear (inverted-U) relationship between working memory and mania in a sample of first-episode patients with slightly more men, potentially accounting for the low explanatory power of affective symptoms in our regression model; a non-linear model may be a better fit and provide additional insight on whether neurocognition and mania are differentially related in men and women. In light of the fact that male and female schizophrenia patients have distinct presentations of affective symptoms (Abel et al., 2010), it is important not to overlook its effect on cognitive functioning.

We also found that medication side effects, more severe in women overall, are more significantly associated with female performance in working memory and speed of processing. After a preliminary analysis (uncorrected for multiple comparisons), significantly more women than men in our sample scored above zero for failing memory (59.6% versus 45.8%), depression (36.8% versus 27.1%), constipation (16.6% versus 5.1%), pruritus (13.5% versus 6.5%), and photosensitivity (22.3% versus 4.5%). Furthermore 28.0% of women also reported amenorrhoea as a side effect, an item not applicable to men. Side effect severity was a significant predictor of processing speed in women, explaining a fair amount of the variance (17%). One might conjecture that subjective report of poor memory and depressive mood has a direct link to worse cognitive performance in tests of processing speed. Given that both subjective report of side effects and processing speed are highly tied to real-world functioning, in order to increase treatment efficacy, it is crucial to address the debilitating influence of side effects in female patients in conjunction with any cognitive therapy.

4.1.4. Disorganisation and DUP

Lastly, we did not observe any correlations between cognitive performance and disorganisation or DUP. Although in contrast to hallucinations and delusions, cognitive correlates have been more reliably reported for disorganisation, we failed to replicate previous associations found between disorganisation and verbal learning/memory, cognitive flexibility and executive control (Galderisi et al., 2009; Lucas et al., 2004). This may be due to the low percentage (less than 10%) of patients expressing any symptoms from that dimension at baseline, which substantially any meaningful conclusions. Another possible confound is the partial loading of the “formal thought disorder” item in SAPS in both “positive symptoms” and “disorganisation” after factor analysis, potentially obscuring associations with cognitive performance.

There were also no significant associations between DUP and neurocognitive domains in either men or women, which lends further credence to the view that the length of untreated psychosis does not have a detrimental effect on cognition in schizophrenia (Goldberg et al., 2009; Lutgens et al., 2014), and that any cognitive deficits are pre-existing and relatively stable once psychotic symptoms have set in (Lewandowski et al., 2011).

4.2. Gender differences in demography, symptomatology and cognition

Men had significantly earlier onset, more education and more negative symptoms in our sample of FEP patients. Younger age of onset in men is a robust finding in schizophrenia research across different countries (Häfner et al., 1998; Vázquez-Barquero et al., 1995). Men display a modal incidence in their teens to early twenties, while women show a greater peak in middle age. Later onset age is generally associated with less genetic loading, more benign course of illness and better prognosis (Abel et al., 2010).

The finding that men had more severe negative symptoms is consistent with other studies on FEP (Chang et al., 2011; Morgan et al., 2008). Likewise, our result that women experienced heavier side effects is also corroborated by the literature (Leung and Chue, 2000). Men had significantly better working memory, in contrast to studies reporting less cognitive impairment in women (Goldstein et al., 1998). The higher educational attainment of men in the current study may have contributed to their superior performance in working memory.

4.3. Limitations

The present study analysed a large representative cohort of adult-onset FEP participants, and found differences in the cognitive profile and associations with symptomatology of male and female patients. However, limitations exist in terms of the analysis being guided by *p*-values, as in a large sample the effect sizes of such significant relationships may be small. Indeed, in the current study most effect sizes save that of the correlation between cognition and education are below medium, suggesting that there are few substantial sex differences in cognition in relation to symptoms and functioning in a large representative sample of adult-onset first episode psychosis patients. Moreover, it may be difficult to generalise our results to the psychosis population in general, as cognition in early-onset and older adult cohorts may display contrasting cognitive profiles and trajectories related to differing neuro-maturational processes underlying psychosis at various life stages. Another limitation may be the cross-sectional design of the study, making it hard to draw conclusions about causal relationships between symptoms and cognition. This underscores the need for more large scale longitudinal studies tracking cognitive changes and the emergence and trajectory of psychotic symptoms in both early and adult onset populations. Furthermore, the inclusion of a control group will help contextualise our findings in view of existing gender differences in cognition.

4.4. Implications for clinical treatment and outcome

Cognitive impairment has been shown to be an important predictor of long-term functioning and outcome, independent of symptomatic severity (Green et al., 2004). In this regard, a combination of psychopharmacological intervention and cognitive remediation has yielded the greatest functional improvements for schizophrenic patients (Wykes et al., 2011). Our results may be the most applicable for the adult-onset, female majority subtype of schizophrenia, as delineated by Castle and Murray (1991). Several studies (Mueser et al., 1995, Penn et al., 1996) have noted a relationship between social functioning and cognitive impairment only in women. The higher levels of correlation we observed between female social functioning, negative symptoms and cognition, particularly executive function, suggest that these aspects are more interrelated than in men.

Compared to the early-onset neurodevelopmental sub-type, characterised by higher proportion of males, greater cognitive impairment and deteriorating illness course, this adult-onset group has more robust personality and cognitive development before onset, making them more amenable to pharmacological and cognitive interventions. Treatment planning for this group should focus on returning patients to their premorbid occupational and social functioning and preventing relapse, while for early-onset patients the emphasis should be placed on symptom management and rehabilitation. In particular, care should be taken to manage and alleviate any medication side effects in female patients, due to the relatively adverse effects they may have on cognition and functioning.

Declaration of interest

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