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Sex Differences in Verbal Memory Predict Functioning Through Negative Symptoms in Early Psychosis

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Verbal memory (VM) is one of the most affected cognitive domains in first-episode psychosis (FEP) and is a robust predictor of functioning. Given that healthy females demonstrate superior VM relative to males and that female patients show less-severe illness courses than male patients, this study examined whether normative sex differences in VM extend to FEP and influence functioning. Four hundred and thirty-five patients (299 males, 136 females) with affective or nonaffective psychosis were recruited from a catchment-based specialized FEP intervention service and 138 nonclinical controls (96 males, 42 females) were recruited from the same community. One of the two neurocognitive batteries comprising six cognitive domains (VM, visual memory, working memory, attention, executive function, processing speed) were administered at baseline. In patients, positive and negative symptoms were evaluated at baseline and functioning was assessed at 1-year follow-up. Patients were more impaired than controls on all cognitive domains, but only VM showed sex differences (both patient and control males performed worse than females), and these results were consistent across batteries. In patients, better baseline VM in females was related to better functioning after 1 year, mediated through fewer baseline negative symptoms. Supplemental analyses revealed these results were not driven by affective psychosis nor by age and parental education. Thus, normative sex differences in VM are preserved in FEP and mediate functioning at 1-year follow-up via negative symptoms. This study highlights the importance of investigating sex effects for understanding VM deficits in early psychosis and suggests that sex may be a disease-modifying variable with important treatment implications.

Key words: first-episode psychosis/cognition/sex effects/outcomes

Introduction

Sex differences are among the most striking demographic characteristics of memory performance in healthy people, found both in the rate and accuracy of memory formation, ie, females outperform males on measures of verbal memory (VM), as well as in the learning strategies males and females differentially employ.[1] This has important implications for understanding psychosis given that VM is one of the most consistently and severely compromised neurocognitive domains[2] and is among the strongest predictors of functioning in this population.[3]

Males with enduring schizophrenia tend to have worse outcomes than female patients,[4] which may be attributable to several risk factors that are more prevalent in males. These include an earlier age at onset, poorer premorbid functioning, higher rates of substance abuse, and more negative symptoms.[5] Across the sexes, negative symptoms and cognitive deficits have been posited to share many features, including a similar onset and temporal course,[6] and both have been shown to correlate with functional outcomes[7] and cortical structure.[8]

In enduring schizophrenia, several studies have demonstrated superior VM performance in female patients compared with male patients,[9,10] consistent with findings in healthy individuals.[1] One study, however, reported the opposite finding,[11] and still others have found no significant sex differences.[12] These inconsistencies may be at least partly attributable to diagnostic heterogeneity between samples; for example, the study reporting superior performance in male patients included diagnoses of both schizophrenia and affective psychosis,[11] whereas studies that reported superior performance in females included diagnoses of schizophrenia only.[9,10] Furthermore, previous studies that failed to detect sex differences in VM were often conducted in multiple-episode patients with more severe deficits and a sustained need for mental

health services; therefore, one possibility is that sex differences at a very low level of functioning in this population are not present or are masked due to floor effects.

Studies of patients at an early stage of the illness have an advantage over studies of patients with longer illness durations by limiting confounding variables such as prolonged exposure to medication, sedentary lifestyle, protracted stigmatization, and the negative effects of multiple hospitalizations. Yet few studies have examined whether sex differences in VM performance are present in individuals with a first episode of psychosis (FEP) and the results of those that remain equivocal, perhaps due to diagnostic heterogeneity or small sample sizes.[13] Interestingly, Zhang et al[14] observed sex effects in enduring schizophrenia patients (n = 960) such that males performed worse than females, despite finding no sex differences in attention and VM performance in a sample of first-episode schizophrenia (n = 262) and matched healthy controls (n = 265). Notably, first-episode males and females in their sample did not differ in terms of psychopathology, whereas chronic male patients had significantly more negative symptoms than female patients, suggesting that negative symptom severity may be related to males' poorer VM performance.

Efforts to assess the relationship between negative symptoms and VM impairments in psychosis suggest that the two are related but separate domains of psychopathology, with the observed association potentially influenced by their shared relationship with other features of the illness, including onset and temporal course.[7] Still, the consistency of the association between negative symptoms and neurocognition,[15] combined with results from studies examining negative symptom remission as a predictor of functional outcomes,[16] raises the possibility that negative symptoms might mediate the observed relationship between VM performance and functioning after a FEP. Although sex differences in functioning and clinical characteristics of psychosis are well established,[17] there lacks a clear understanding of how negative symptoms and VM deficits might differentially affect male and female patients. Given that males are typically overrepresented in schizophrenia samples, it is possible that male patients chiefly contribute to the observed associations between negative symptoms and neurocognitive impairments reported in studies where the effects of sex were not explicitly examined.

The present study, which builds on a large and well-characterized FEP dataset presented in previous work[3,18–20] and presents our largest sample to date, investigates whether there are sex differences in VM in FEP patients compared with nonclinical healthy individuals and whether such differences interact with negative symptoms to influence functioning. Previous studies examining sex differences in neurocognition have reported inconsistent results[11,12,21] and have been limited by the range of cognitive domains assessed, making it difficult to establish the specificity of any observed sex effects. Thus, although the current investigation focuses on VM due to the well-established sex effect in healthy samples[1] and it being a strong predictor of outcome in psychosis,[3] we also examined sex differences across a range of cognitive domains (VM, visual memory, working memory, attention, executive function, processing speed). We hypothesized similar sex differences in VM (females > males) in FEP patients and nonclinical controls. We did not expect to observe sex differences in the other neurocognitive domains assessed due to the inconsistency of previous findings.[12,21] Furthermore, based on the strength of the relationship between VM and negative symptoms and between negative symptoms and outcome, we hypothesized that baseline VM performance and negative symptoms would mediate the relationship between sex and functioning at 1-year follow-up. Finally, given that diagnostic heterogeneity is a source of variability in previous studies examining sex differences in cognition, we also re-conducted all analyses in schizophrenia spectrum patients only.

Methods

Participants

FEP patients (299 males, 136 females) were recruited between 2003 and 2018 from the Prevention and Early Intervention Program for Psychosis (PEPP-Montreal), a specialized early-intervention service for individuals who have recently experienced a FEP within a local catchment area of Southwest Montreal, QC, Canada. Subsets of this dataset have been published previously by ours[3,18,19] and other[22,23] PEPP-Montreal research groups, though none looking at sex differences in cognition. The present study reports on our largest sample to date and, to our knowledge, is the most comprehensive dataset used to investigate cognitive sex differences in FEP patients recruited from a single site. FEP patients included in the present study were between the ages of 18 and 35, had a diagnosis of affective or nonaffective psychosis, an IQ > 70, and no past antipsychotic medication treatment for >1 month. Nonclinical controls (96 males, 42 females) were also recruited from the community and were matched for age, sex, and education level to the patient group at recruitment. Sex, but not age or education, matching was retained after excluding participants with missing data and this is addressed in supplemental analyses. Exclusion criteria for healthy controls included history of Axis I disorders, neurological disease, or traumatic brain injury, and first-degree family history of schizophrenia or related schizophrenia spectrum psychosis. All participants provided written informed consent, and the research protocol was approved by the Douglas Mental Health University Institute human ethics review board.

Measures

The following variables were collected for both patients and controls at the time of neurocognitive testing: age, years of education, and full-scale IQ measured with the Wechsler Abbreviated Scale of Intelligence.[24] Diagnoses were established with the Structured Clinical Interview for DSM-IV.[25] The Scale for the Assessment of Positive Symptoms (SAPS)[26] and the Scale for the Assessment of Negative Symptoms (SANS)[27] were administered by trained research staff to measure baseline symptom severity in patients (mean [SD] 14.22 [14.62] days between neurocognitive assessments and symptom evaluations). The SANS attention domain was excluded given previous research demonstrating it does not load strongly onto negative symptom clusters.[28] Baseline depressive symptoms in patients were assessed with the Calgary Depression Scale for Schizophrenia.[29] Age at onset of psychosis (age at first appearance of threshold-level psychotic symptoms) and duration of untreated psychosis (DUP; time between first psychotic episode to administration of adequate treatment) were both determined using the Circumstance of Onset and Relapse Schedule, which includes material adapted from the Interview for Retrospective Assessment of Onset of Schizophrenia.[30] Antipsychotic dosage at baseline was recorded and converted to chlorpromazine equivalents.[31]

Neurocognitive assessments were administered at baseline in pen and paper format with the Wechsler Memory Scale—Third Edition (WMS-III)[32] to participants recruited between 2003 and 2010 (FEP: males = 176, females = 79; nonclinical controls: males = 47, females = 22) and in computerized format with the CogState Research Battery (CSRB)[33] to participants recruited thereafter (FEP: males = 123, females = 57; nonclinical controls: males = 49, females = 20). For a complete list of neurocognitive tests included in each battery, see supplementary table 1. Notably, the 2 batteries differ according to the type of VM task used, where the WMS-III includes a story recall task and the CSRB includes a word-list learning task.

Baseline neurocognitive assessments took place when patients were in a stable but not necessarily asymptomatic condition (approximately 3 months following admission to PEPP). Control average *z*-scores were used as normative data to transform individual patient data into battery-specific *z*-scores. A composite score was calculated for each cognitive domain in both neurocognitive batteries by averaging z-scores for all tests within each domain.[18] Functioning was assessed one year after treatment (combined medication and psychosocial approaches tailored to patients' specific needs[34]) with the Social and Occupational Functioning Assessment Scale (SOFAS).[35]

Statistical Analyses

Differences in demographic and clinical characteristics between males and females within each group (FEP and nonclinical controls) were tested with unpaired *t*-tests, χ^2 tests, and Mann–Whitney tests as appropriate. An ANCOVA was applied to evaluate the main effects of sex and group, as well as their interaction, on each neurocognitive domain, covarying for battery type (WMS-III, CSRB). In a previous study, Benoit et al[18] revealed a significant difference in VM deficits between batteries (ie, patients performed better for list [CSRB] versus story [WMS-III] recall);, therefore, we also examined the neurocognitive batteries separately with ANOVAs, entering sex and group as between-subject factors. This allowed us to examine whether sex differences replicated across the 2 batteries.

Given that there were sex differences in education in our sample, and that education is strongly related to cognition, we also controlled for education to ensure that any observed sex effects on VM were not solely attributable to sex differences in education. Although it is best to match groups on parental education since psychosis can interrupt educational attainment, these data were limited for a large portion of our patient sample. We thus conducted an exploratory analysis of sex and group effects on cognition in a subsample of FEP and controls matched on parental education (and age, given the observed group difference in this variable; see supplementary table 5).

To test our mediation model, analyses were conducted using PROCESS,[36] a toolbox in SPSS that generates direct and indirect effects of independent variables in a variety of moderation and mediation models. Specifically, we tested whether the impact of sex on functioning after 1 year of treatment was mediated by VM (mediator 1; M1) and negative symptoms (mediator 2; M2) after controlling for years of education. Notably, the mediation analysis was performed with a subsample (189 males, 100 females) of the original patient group due to missing data. All statistical tests were performed on SPSS version 22 (SPSS) and were 2-tailed with an alpha level of .05.

Results

Demographic/Clinical

Demographic and clinical characteristics of participants are shown in table 1. There were no significant differences in the sex distribution in the 2 groups ($\chi^2 = 0.03$, $p = .85$). There were statistically significant main effects of group on demographic variables, such that FEP patients were younger ($\eta^2 = 0.01$), had fewer years of education ($\eta^2 = 0.09$), and had lower IQ ($\eta^2 = 0.10$) than nonclinical controls. There was also a statistically significant main effect of sex on years of education, with males having fewer years of education than females ($\eta^2 = 0.02$). For clinical variables, female patients had more pronounced depression compared to male patients, ($t(228) = -3.13$, $p < .01$). Correlations were explored between depression scores and cognitive performance, yielding nonsignificant coefficients ($ps > .15$) and therefore were not included as

Table 1. Sample Characteristics

	FEP patients				Nonclinical controls			
	Males (n = 299)		Females (n = 136)		Males (n = 96)		Females (n = 42)	
Variable	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age (y)[a]	23.23	4.42	23.46	4.71	24.55	5.43	24.25	4.45
Education (y)[ab]	11.84	2.55	12.71	2.59	13.74	2.38	14.56	2.07
IQ[a]	97.53	15.57	96.76	14.27	111.18	14.79	107.79	13.38
	Mean	SD	Mean	SD				
Age at onset (y)	22.31	4.36	22.40	5.47	—	—	—	—
CPZ at baseline	179.00	139.00	158.00	138.00	—	—	—	—
SAPS	14.43	14.24	16.54	16.82	—	—	—	—
SANS	23.09	13.82	21.68	13.82	—	—	—	—
CDSS[b]	2.50	3.98	3.92	4.50	—	—	—	—
SOFAS at 1 y	61.98	17.04	63.27	18.50				
	Median	IQR	Median	IQR				
DUP (wk)	16.14	4.57–60.22	14.29	5.36–41.93	—	—	—	—
	N	%	*N*	%				
Schizophrenia spectrum								
Schizophrenia	139	46.49	43	31.62	—	—	—	—
Schizoaffective	23	7.69	14	10.29	—	—	—	—
Delusional disorder	7	2.34	2	1.47	—	—	—	—
Brief psychotic disorder	1	0.33	0	0.00	—	—	—	—
Psychosis NOS	31	10.37	16	11.76	—	—		
Affective psychosis	41	13.71	20	14.71	—	—		
Bipolar disorder								
Major depression with psychotic features	25	8.36	16	11.76	—	—	—	—
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Cognitive domain								
Verbal memory[ac]	−1.16	1.14	−0.33	0.96	−0.15	0.93	0.35	0.75
Visual memory[a]	−0.75	1.13	−0.54	1.11	−0.03	0.86	0.11	0.77
Working memory[a]	−0.63	0.98	−0.51	0.83	0.03	0.83	−0.10	0.93
Attention[a]	−0.57	1.21	−0.41	1.13	−0.04	0.94	0.09	1.11
Executive function[a]	−0.87	1.25	−0.68	1.19	0.04	0.87	0.04	0.72
Processing speed[a]	−0.33	1.15	−0.64	1.01	0.06	0.87	−0.14	0.83

Note: CDSS = Calgary Depression Scale for Schizophrenia, total score; CPZ = chlorpromazine hydrochloride equivalents; SANS = Scale for the Assessment of Negative Symptoms, sum of total scores for each subscale; DUP = duration of untreated psychosis; IQR = interquartile range; SAPS = Scale for the Assessment of Positive Symptoms, sum of total scores for each subscale; SOFAS = Social and Occupational Functioning Assessment Scale.
[a]Significant group difference ($p < .05$).
[b]Significant sex difference ($p < .05$).
[c]Significant sex difference ($p < .01$).

covariates in the main analyses. Males and females within the patient group had comparable ages at onset, medication dosage, positive and negative symptoms, DUP, and distribution of diagnoses (ps > .05). Comparison of schizophrenia spectrum and affective psychosis patients on demographic and clinical variables also revealed no sex differences in either diagnostic group (see supplementary table 3), although schizophrenia spectrum patients (males and females combined) exhibited a significantly longer DUP than patients with affective psychosis (group median, 18.71 weeks [interquartile range, 7.64–65.50 weeks] vs 7.29 weeks [interquartile range, 2.15–18.15 weeks]; $p < .01$). Also, depression scores were higher in affective patients ($F(1,370) = 14.60$, $p < .01$) and more severe in females in both groups ($F(1,370) = 5.90$, $p < .05$). Finally, the sample included in the mediation analysis did not differ in demographic and clinical characteristics at baseline from the sample excluded owing to incomplete SOFAS data at 1-year follow-up (supplementary table 2).

Effects of Sex and Group Across Neurocognitive Domains

Sex and group differences in FEP patients and nonclinical controls for each neurocognitive domain are displayed in figure 1. There was a significant main effect of sex on VM across both groups such that males performed more poorly than females, $F(1,568) = 31.62$, $p < .01$, whereas performance on all other cognitive domains did not significantly differ between sexes (ps > .05). A main effect of group demonstrated that patients were more impaired than nonclinical controls across all 6 neurocognitive

domains assessed (all *p*s < .01). No significant sex × group interactions were observed for any neurocognitive domain (*p*s > 0.15). Main effects of sex and group on VM performance also emerged for both batteries when examined separately (figure 2). Specifically, males performed worse than females (WMS-III: $F(1,320) = 15.40$, $p < .01$; CSRB: $F(1,245) = 16.50$, $p < .01$) in both groups, and patients performed worse than controls (WMS: $F(1,320) = 60.48$, $p < .01$; CSRB: $F(1,245) = 19.06$, $p < .01$). No sex × group interactions were present in either battery (ps > .32). Finally, the same pattern of sex differences was observed across diagnoses (supplementary figure 1) and in the subsample matched on age and parental education (supplementary figure 2).

Functioning After 1 Year of Treatment

Mediation analysis revealed that male sex predicted worse VM performance ($a_1 = 0.63$), which predicted more negative symptoms ($a_3 = -2.66$), which in turn predicted poorer functioning after 1 year of treatment ($b_2 = -0.31$) (table 2, figure 3). The *total effect* of sex on functioning (without including the mediators in the model) was nonsignificant (β = 0.96, SE = 0.93, 95% confidence interval [CI] = [−0.86, 2.79]). There was also no significant *direct effect* of sex on functioning (β = 0.29, SE = 2.41, 95% CI = [−4.53, 4.96]). Education was a significant covariate in the model, predicting both better VM performance (β = 0.13, SE = 0.03, 95% CI = [0.07, 0.18]) as well as improved functioning at 1-year follow-up (β = 1.42, SE = 0.45, 95% CI = [0.53, 2.31]). Examining the 3 *specific indirect effects* revealed that the mediation model "sex → VM → negative symptoms → functioning" was significant (β = 0.53, SE = 0.26, 95% CI = [0.12, 1.12]). The other 2 specific indirect effects, "sex→ VM → functioning" (β = 0.63, SE = 0.72, 95% CI = [−0.78, 2.12]) and "sex→ negative symptoms → functioning" (β = −0.19, SE = 0.57, 95% CI = [−1.38, 0.91]), were both not significant—that is, neither VM nor negative symptoms alone mediated the relationship between sex and functioning at 1-year follow-up. Education was a significant covariate in the model, predicting both better VM performance

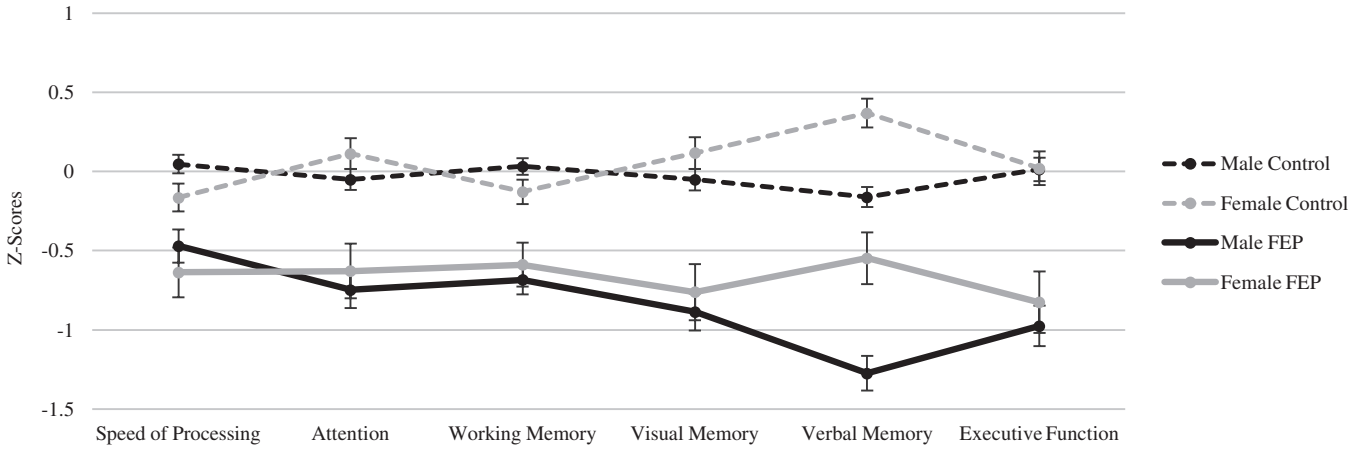

Fig. 1. *z*-Scores for neurocognitive domains by sex and group. Significant sex difference in verbal memory *z*-score ($p < .01$). Significant group difference across all cognitive domains ($p < .05$).

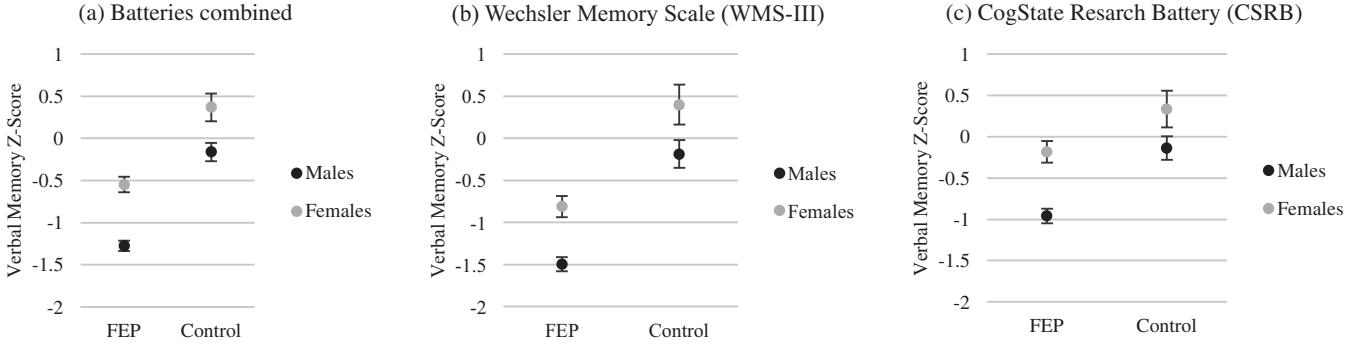

Fig. 2. Verbal memory performance by sex and group. (a) Batteries combined. Significant sex difference in verbal memory *z*-score ($p < .01$). Significant group difference in verbal memory *z*-score ($p < .01$). (b) Wechsler Memory Scale (WMS-III). Significant sex difference in verbal memory *z*-score ($p < .01$). Significant group difference in verbal memory *z*-score ($p < .01$). (c) CogState Research Battery (CSRB). Significant sex difference in verbal memory *z*-score ($p < .01$). Significant group difference in verbal memory *z*-score ($p < .01$).

Table 2. Significant Variables Within Mediation Model

Outcome	Variable	Path	β	SE	*p*	Model R^2
Verbal memory	Sex	a_1	0.63	0.15	<.01	.19
	Years of education		0.13	0.03	<.01	
Negative symptoms	Sex	a_2	0.62	1.85	.74	.08
	Verbal memory	a_3	−2.66	0.82	<.01	
	Years of education		−0.54	0.34	.12	
Functioning	Sex	C	0.22	2.41	.93	.14
	Verbal memory	b_1	1.00	1.09	.36	
	Negative symptoms	b_2	−0.31	0.09	<.01	
	Years of education		1.42	0.45	<.01	

Note: Sample size for mediation model included 189 males and 100 females.

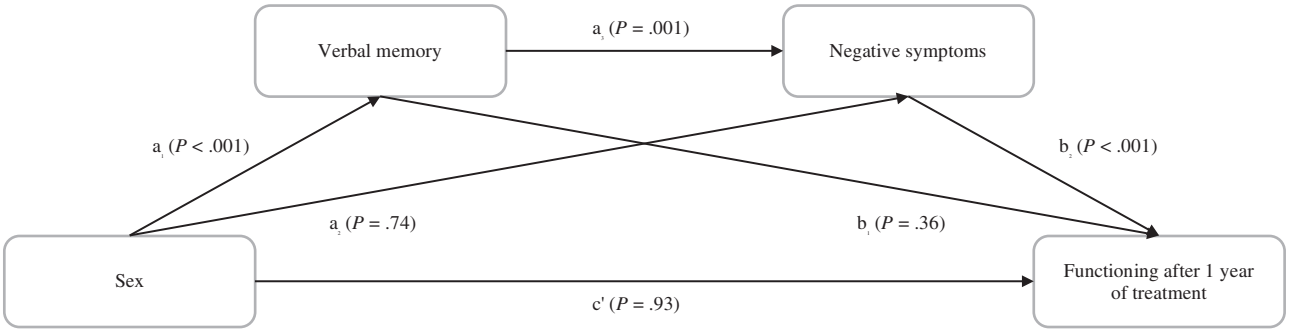

Fig. 3. Mediation model illustrating association between sex and functioning at 1-year follow-up. For the categorical variable sex, males were coded as 0 and females as 1. Therefore, a positive β value for a_1 (as was reported) indicated that females had greater verbal memory scores compared with males.

(β = 0.13, SE = 0.03, 95% CI = [0.07, 0.18]) as well as improved functioning at 1-year follow-up (β = 1.42, SE = 0.45, 95% CI = [0.53, 2.31]). Finally, results were identical in schizophrenia spectrum group subsample (supplementary table 4), ie, the serial mediation model "sex → VM → negative symptoms → functioning" was significant (β = 0.67, SE = 0.38, 95% CI = [1.00, 1.57]), as well as in the subsample of patients matched on age and parental education were analyzed (supplementary table 6), ie, the serial mediation model "sex→ VM → negative symptoms → functioning" was significant (β = 0.74, SE = 0.41, 95% CI = [0.13, 1.66]).

Discussion

The goal of the present study was to evaluate whether sex differences in VM performance observed in healthy subjects are also present in FEP patients, and how such differences relate to functioning after 1 year of treatment. A tertiary aim was to report on FEP sex differences in other cognitive domains using this large sample as previous findings have been inconsistent. Patients were impaired on all neuropsychological domains, with deficits most pronounced in VM, a finding supported by others.[37] Importantly, VM was the only cognitive domain for which performance differed significantly between the sexes, with females outperforming males in both groups. The lack of an interaction effect between sex and group observed in this study and by others[21] corroborates the notion that the female VM advantage in FEP is comparable to that seen in healthy individuals. This sex effect was evident for both story recall and word-list recall tests of VM and was likely not due to sex differences in other cognitive processes (eg, attention, processing speed) as these did not differ between sexes. Notably, all FEP patients were treated for only a short period of time prior to the baseline assessment of neurocognition and symptoms, restricting confounding effects of medication. This is especially important given that most antipsychotic medications act via the sexually dimorphic dopaminergic system.[38] Thus, the observed VM sex difference in our sample extends findings of superior VM performance in healthy females relative to males by showing that this pattern also exists in FEP and is not the result of measure variability or associated clinical and cognitive factors.

With respect to functioning, our results suggest that the propensity for poorer functional outcome among males is mediated by sex differences in VM deficits through negative symptomatology. The association between VM impairments and negative symptoms has been well-documented during the early stages of psychosis,[15] and both have been linked to functional outcomes,[3] raising questions about their possible interactions. However, the degree of overlap between negative symptoms and

cognition remains unclear. In this study, we demonstrated that the relationship between sex and functioning after 1 year of treatment was mediated by VM ability, which in turn predicted negative symptom severity. In fact, neither VM nor negative symptoms alone mediated the relationship between sex and functioning. Overall, our mediation model supports the theoretical possibility that negative symptoms might be at least in part a consequence of cognitive impairments rather than a cause, in keeping with the results from Harvey et al,[6] suggesting that neuropsychological performance is related to the *ability* to perform everyday living skills, while negative symptoms are associated with the *likelihood* of performing such skills. As such, males' greater negative symptom severity might hinder their ability to effectively engage with interventions aiming to improve functional outcomes during their first year of treatment. Lending biological support to this model of psychosis, a recent study from our group observed that patients with a worsening course of negative symptoms and VM had increased divergence of microstructure within the hippocampal circuit from other cortical regions.[39] Specifically, they showed that VM mediated the association between reduced centrality of the hippocampal circuit and negative symptoms, highlighting the interplay between VM and negative symptoms at the level of the brain. Given that negative symptoms are difficult to treat, these results highlight VM deficits as a treatment target with enhanced therapeutic potential.

Considerations of the asymmetric effect of sex on healthy brain development has led to compelling theories about how and why male and female brains might differ in their vulnerability or resilience to psychosis. For instance, Wong and Weickert[40] suggested that brain development, which is differentiated at conception through sex-chromosomal marking, interacts with specific hormonal exposure during critical periods of neurodevelopment. Interestingly, many of the brain regions that have been shown to differ between males and females, including frontal, temporal, and hippocampal areas,[41] also show structural differences between typically developing individuals and persons with schizophrenia,[42] providing some basis for the view that a common mechanism driving the risk for developing psychosis in early adulthood in males and females becomes differentially influenced by sex. Developmental risk factors for psychosis such as prenatal and early-life stress[43] have been shown to affect signaling pathways implicated in long-term potentiation, anatomy of memory-related brain areas, and memory function.[44] These effects are facilitated by gonadal and adrenal hormones and therefore depend on the sex of the individual. As such, sex-mediated neurodevelopmental processes that affect both risk for psychosis and memory function may do so through quantifiable changes in brain regions in a sex-dependent way and warrant further investigation.

Despite the consistency of the present findings with most previous investigations of sex differences in neurocognitive functioning in FEP and enduring psychosis,[21] they are in contrast with other reports in which male patients outperform females on tasks of both verbal and visual memory, as well as attention,[11,12] and thus merit future research. Discrepant findings in the literature may also be due to poor sampling strategies leading to sex differences in demographic characteristics, age at onset, and psychopathology.[14,45] They might also arise from previously underpowered studies due to small sample sizes for detecting sex effects or from the absence of healthy comparison subjects to evaluate whether sex differences in clinical populations are consistent with those already established in healthy cognitive functioning.[12,45] In our well-characterized sample of FEP patients, males and females did not differ in severity of positive or negative symptoms at baseline, nor in terms of age at onset or DUP, suggesting that sex differences in VM are present even in the absence of these confounds. In fact, the female advantage in VM was observed in both schizophrenia spectrum and affective psychosis samples.

To the best of our knowledge, this is the largest study to date examining sex differences in neurocognitive performance in a well-characterized sample of FEP patients relative to nonclinical controls. Data were obtained from the sole specialized early-intervention service within the local catchment area, making the sample epidemiologically representative. Furthermore, no significant differences in baseline demographic or clinical characteristics were found between participants included in our mediation analysis and those excluded due to incomplete functioning data at 1-year follow-up (supplementary table 2). This finding suggests that the 289 patients (189 males, 100 females) studied were fairly representative of the total clinical population being served and that the findings are relatively generalizable. Still, our results should be interpreted in the context of several limitations. First, the cross-sectional nature of our cognitive measurement limits our understanding of how VM deficits might differentially affect males and females across disease stages. Also, given that negative symptoms are expected to fluctuate over time, longitudinal assessments of cognition are needed to assess the influence of VM on male and female patients' response to treatment (ie, remission or reduction in negative symptoms). Indeed, it is likely that VM has a large influence on patients' response to treatment early on and that this enhanced response to treatment then has a greater impact on functioning in the longer term. Furthermore, the path from sex differences in cognition to functioning in psychosis likely involves a complex interplay of many factors (eg, social cognition) and warrants further investigation. Additionally, years of education, which correlates strongly with neurocognitive performance, differed between males and females in both groups in our sample. Covarying for this variable, however, did not change our results, suggesting that sex differences in VM are not merely a reflection of differences in

levels of educational attainment. Future research should, however, consider matching participants on parental rather than personal education, given that psychosis can disrupt educational attainment. Furthermore, neuropsychological performance in females has been shown to fluctuate with their menstrual cycle,[46] which was not controlled for in this study. Also, because our aim was to specifically examine the relationship between biological sex, VM, and functioning, we did not consider the relative contribution of gender identity. Further, we acknowledge the limitation that our original research protocol did not systematically collect data on race/ethnicity, which should be considered in future research. Finally, although the SOFAS is a useful tool to measure social and occupational functioning independent of patients' overall symptom severity, it is limited as a clinician-rated subjective measure. Future research should examine both objective (eg, employment, independent living, etc.) and subjective measures of functioning.

In conclusion, the results of the present investigation suggest that normative sex differences in VM are preserved in FEP and mediate functioning at 1-year follow-up through negative symptom severity. Thus, consideration of sex effects is important in the context of understanding VM deficits in psychosis and suggests that sex may act as a disease-modifying variable with important treatment implications. To date, guidelines for the treatment of psychosis have not directly distinguished between the sexes. Recognizing ways in which the needs of individuals with psychosis differ as a result of their biological sex provides an important opportunity to deliver high-quality, patient-oriented care and thus the potential for better outcomes for this illness.

Supplementary Material

Supplementary data are available at *Schizophrenia Bulletin* online.

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