Sex differences in cognitive functioning in at-risk mental state for psychosis, first episode psychosis and healthy control subjects

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Abstract

Background

Several sex differences in schizophrenia have been reported including differences in cognitive functioning. Studies with schizophrenia patients and healthy controls (HC) indicate that the sex advantage for women in verbal domains is also present in schizophrenia patients. However, findings have been inconsistent. No study has yet analysed sex-related cognitive performance differences in at-risk mental state for psychosis (ARMS) individuals. Thus, the aim of the present study was to investigate sex differences in cognitive functioning in ARMS, first episode psychosis (FEP) and HC subjects. We expected a better verbal learning and memory performance of women in all groups.

Methods

The neuropsychological data analysed in this study were collected within the prospective ***F***rüh***e***rkennung von ***Psy***chosen ***(FePsy)*** study. In total, 118 ARMS, 88 FEP individuals and 86 HC completed a cognitive test battery covering the domains of executive functions, attention, working memory, verbal learning and memory, IQ and speed of processing.

Results

Women performed better in verbal learning and memory regardless of diagnostic group. By contrast, men as compared to women showed a shorter reaction time during the working memory task across all groups.

Conclusion

The results provide evidence that women generally perform better in verbal learning and memory, independent of diagnostic group (ARMS, FEP, HC). The finding of a shorter reaction time for men in the working memory task could indicate that men have a superior

working memory performance since they responded faster during the target trials, while maintaining a comparable overall working memory performance level.

Key words: Schizophrenia; cognition; gender differences; clinical high-risk

1. Introduction

Sex differences in schizophrenia are described in almost all aspects of the illness, including age of onset, symptomatology, treatment response, time course and psychosocial outcome [1-3]. One of the most consistent findings is that women are older than men when first symptoms arise [4, 5]. Furthermore, women – especially at younger ages – seem to have a more favourable outcome than men [2, 6].

Closely related to the outcome of the disease is the impairment of cognitive functioning which is recognized as a core feature of schizophrenia [7, 8] that is not only present in patients with schizophrenic psychoses, but already evident in individuals with an at-risk mental state (ARMS) for psychosis [9-11]. In addition, it has been shown that ARMS individuals with later transition to psychosis perform worse on tests measuring verbal fluency and memory [9, 12] and speed of information processing [13, 14] compared to those without transition. It has been consistently reported that prediction of psychosis can be improved by considering neurocognitive performance measures [14, 15]. However, deficits in specific cognitive domains among ARMS and schizophrenia patients are at least in part explained by differences in IQ [Referenz einfügen].

Sex differences in cognitive functioning are well known in healthy individuals. In general, women tend to perform better than men in tasks measuring verbal abilities, whereas the opposite is true for visuospatial skills [16-19]. Kimura suggested that tasks measuring verbal memory account for the most prominent sex differences [20].

Differences in cognitive functioning between men and women have also been reported in schizophrenia patients. Many studies have shown that women with schizophrenia perform better than men with schizophrenia in the domain of verbal learning and memory [21-28] which is in line with findings in healthy controls (HC). In other cognitive domains, however, results have been largely heterogeneous. In the domain of executive functions, two studies have demonstrated that women with schizophrenia perform better as compared to men with schizophrenia [21, 29], two studies showed a worse performance of female patients as compared to male patients [22, 30] and three studies did not find any performance

differences [24, 25, 31]. In the domain of attention, two studies showed a better performance of women in relation to men with schizophrenia [21, 28], one showed a worse performance of female patients [32] and five studies could not detect any sex differences [23-26, 33]. With regard to working memory, one study found that women with schizophrenia perform worse, while three studies did not detect any performance differences. Interestingly, when comparing clinical with healthy control samples, Longenecker et al. reported an interaction effect in the working memory domain: Men with schizophrenia failed to exhibit the sex advantage during a working memory task which was evident in the healthy control sample [27]. In relation to IQ estimates, three studies out of four showed an equal performance for both sexes of schizophrenia patients [25, 33, 34]. For speed of processing, there is one study which showed a better performance for women [23] and one study which depicted no sex difference in schizophrenia patients [24].

Since cognitive impairment is recognized as a core feature of schizophrenia, sex differences in cognitive functioning could contribute to explaining pathogenic mechanisms of the illness. However, most of the above named studies were conducted in chronic and/or medicated patients whose neurocognitive performance might thus have been influenced by the effects of medication or chronicity. No study has yet analysed sex-related cognitive performance differences in ARMS individuals and first episode psychosis (FEP) patients. Thus, the aim of the present study was to investigate sex differences in cognitive functioning in ARMS, FEP and HC subjects and whether sex differences vary between the examined groups. Based on the above cited studies, we expected a better performance of women in the domain of verbal learning and memory in all groups.

2. Methods

Setting and recruitment

The neuropsychological data analysed in this study were collected within the prospective ***F***rüh***e***rkennung von ***Psy***chosen ***(FePsy)*** study, which aims to improve the early detection of psychosis. A more detailed description of the overall study design can be found elsewhere

[35, 36]. Participants were recruited for the study via the ***FePsy*** Clinic at the Psychiatric University Outpatient Department of the Psychiatric University Clinics Basel, which was set up specifically to identify and treat individuals in the early stages of psychosis.

We recruited a sample of HC from trade schools, hospital staff and through advertisements. HC subjects with a current or former psychiatric disorder or neurological disease, serious medical condition, substance abuse, or a family history of psychiatric disorder were excluded.

The study was approved by the ethics committee of the University of Basel and all participants provided written informed consent.

Screening procedure

Screening was performed with the Basel Screening Instrument for Psychosis [37]. This instrument allows the rating of individuals regarding the inclusion/exclusion criteria corresponding to the Personal Assessment and Crisis Evaluation (PACE) criteria [38, 39] and has been shown to have a good interrater reliability (κ=0.67) for the assessment of the main outcome category “at risk for psychosis” and a high predictive validity [37]. Individuals were classified as being in an ARMS for psychosis, having a FEP, or being not at risk for psychosis (usually other psychiatric disorders). We included ARMS, FEP as well as a sample of HC in the present study.

Neuropsychological assessment

All neuropsychological assessments were conducted by psychologists and well-trained, supervised advanced psychology students. The test battery covered the following domains: general intelligence, executive functions, working memory, attention, verbal learning and memory [35, 36].

General intelligence was estimated with the Mehrfachwahl-Wortschatz Test (MWT-A)[40] and the Leistungsprüfsystem, scale 3 [41], which are well established German intelligence scales for assessing verbal and nonverbal (abstract reasoning) abilities.

Executive functions were assessed with the Tower of Hanoi (ToH) [42], Wisconsin Card Sorting Test (WCS) [43, 44], and Go/No-Go subtest of the Test of Attentional Performance (TAP) [45].

Working memory was measured with the 2-back task of the TAP [45] and vigilance with the Continuous Performance Test (CPT-OX) [46].

Verbal learning and memory were assessed with the California Verbal Learning Test (CVLT) [47].

For the Go/No-Go subtest and the 2-back task of the TAP as well as for the CPT-OX Test that requires subjects to discriminate between two possible stimuli, we used the Signal Detection Theory (SDT) to measure performance in terms of "response bias" and "sensitivity". Response bias reflects the tendency to respond with yes and was quantified by the measure c, whereas sensitivity indicates the degree of overlap between the signal and the noise distributions and was quantified by the measure d'. Both measures were calculated according to the formulas provided in Wright [48] using the R package sdtalt [48]. The main advantage of using SDT measures is the separation of response bias and sensitivity [49].

A summary cognitive score was calculated by performing a principal component analysis on the test scores of the above described tasks and extracting the factor scores of the first principal component. Thus, test scores were integrated in the summary score with different weights, depending on how much they loaded on the first principal component. The first principal component explained 22% of the total variance.

Psychopathological assessments

Positive psychotic symptoms (i.e., hallucinations, suspiciousness, unusual thought content and conceptual disorganisation) were assessed with the Brief Psychiatric Rating Scale (BPRS) [50, 51] and negative symptoms with the Scale for the Assessment of Negative Symptoms (SANS) [52].

Statistical analyses

All data were analysed using the R environment for statistical computing [53]. Differences in sociodemographic and clinical characteristics between men and women within each diagnostic group (ARMS, FEP, HC and total group) were tested with *t* and χ^2 tests.

The following procedure was applied to investigate the effects of sex (men, women) and diagnostic group (ARMS, FEP, HC) on cognitive functioning. All of the 25 dependant variables, reflecting cognitive functioning were screened for outliers. Values that were 3 standard deviations above or below the mean were treated as missing if they could be attributed to misunderstanding of instructions or truncated (i.e., replaced by the mean ± 3 standard deviations) if no obvious cause for their emergence could be found. The Box-Cox transformation [54] was applied to the outcome measures which did not conform to assumptions of normality and/or homogeneity of variance. The Box-Cox procedure automatically selects exponential transformations that are optimal with regard to normalizing distributions and equalizing variances (Supplementary Table 1).

Since some of the outcome measures contained missing data (Supplementary Table 1), we next performed multiple imputation (MI) using the Multivariate Imputation by Chained Equations software [55]. MI is considered the method of choice of handling complex incomplete data problems because it yields unbiased parameter estimates and standard errors under a missing at random (MAR) or missing completely at random (MCAR) missing data mechanism and maximizes statistical power by using all available information [56].

We generated 100 imputations of the missing values such that 100 completed datasets were obtained to protect against a potential power falloff from a too small number of imputations [57]. The analyses of interest were then conducted in each completed data set and parameter estimates were pooled according to Rubin's rules [58].

Analyses of covariance models (ANCOVA) were applied to evaluate the main effects of sex and group (ARMS, FEP, HC) as well as their interactions on cognitive functioning. We included sex and diagnostic group (ARMS, FEP, HC) as between subject factors and influence of age, years of education and use of antipsychotics as covariates. In case of

significant interaction between sex and diagnostic group, sex differences were explored within each diagnostic group separately. The results are presented with and also without correction for multiple testing. Each table contains a column with the uncorrected and a column with the corrected *p*–values (Benjamini and Hochberg correction) [59].

3. Results

Sample description

136 ARMS individuals and 104 FEP patients were recruited for the ***FePsy*** study from March 1, 2000 to November 1, 2013. We also recruited a sample of 97 HC participants. We excluded 18 ARMS, 16 FEP and 11 HC because their cognitive performance measures were not assessed.

Thus, we performed the analysis on the remaining sample consisting of 118 ARMS, 88 FEP and 86 HC subjects. The excluded individuals did not differ from the included ones with regard to sex, age, years of education, BPRS total score, BPRS Psychosis/Thought Disturbance [49] and SANS total score. Sociodemographic as well as clinical characteristics of the included individuals are presented in Table 1. There were no sex differences in ARMS, FEP, HC and in the total group with regard to age, years of education, use of antipsychotics, BPRS total score and SANS total score except for more pronounced Psychosis/Thought Disturbance of women in the total group (ARMS + FEP) and an older age of women in the HC group.

Insert Table 1 about here

Effects of sex and diagnostic group on cognitive functioning

Sex differences between men and women in the total group as well as within each diagnostic group separately for each cognitive performance measure are displayed in Figure 1. In the ANCOVA model used, diagnostic group (ARMS, FEP, HC) and sex served as between subject factors with age, years of education and use of antipsychotics being

selected as covariates. There was one significant interaction effect in verbal IQ (p = 0.028) (Table 2) which was due to a non-significantly worse performance of women in the ARMS (d = -0.286) (Supplementary Table 2) and FEP group (d = -0.168) (Supplementary Table 3) and a non-significantly better performance in the HC group (d = 0.177) (Supplementary Table 4). However, this interaction was no longer significant after correction for multiple testing.

Insert Figure 1 about here

Insert Table 2 about here

Effects of diagnostic group are presented in Table 2 and have already been described previously [60]. We will not describe this aspect any further because it is not the focal point of the present study.

In the total group (ARMS+FEP+HC), women remembered more words in the CVLT trials 1-5 (p = 0.046, d = 0.258) (Table 2, Supplementary Table 5) and showed less retroactive interference (i.e., influence of newly learned words on the recall of previously learned words) (p = 0.048, d = 0.270) (Table 2, Supplementary Table 5). By contrast, in the total group men demonstrated a shorter working memory reaction time (p = 0.046, d = -0.236) (Table 2, Supplementary Table 5). However, all these significant sex differences did not withstand correction for multiple testing.

Considering each group separately there were no sex differences in ARMS and FEP (Supplementary Table 2 and Supplementary Table 3). In the group of HC, there was only one significant sex difference. Specifically, men demonstrated less response bias in the Go/NoGo task (p = 0.011, d = -0.352) (Supplementary Table 4), but only if uncorrected for multiple testing.

4. Discussion

To the best of our knowledge, this is the first study investigating sex-related neurocognitive performance differences in a sample of HC, ARMS and FEP patients. In line

with our hypothesis, we found that women perform better in the domain of verbal learning and memory independent of diagnostic group. Furthermore, men as compared to women showed a shorter reaction time in the working memory task. Additionally, we found a sex × group interaction effect on verbal IQ, which was due to a non-significantly worse performance of women in the ARMS and FEP group and a non-significantly better performance in the HC group. All these results, however, did not withstand correction for multiple testing. Given that sex-related cognitive performance differences have been found to be rather small [61], we decided to discuss findings that were only significant at an uncorrected level to account for potential false negative results.

Our finding that women perform better in the domain of verbal learning and memory across all diagnostic groups is consistent with a large body of evidence [16, 24, 27, 62, 63]. Since we did not find an interaction between diagnostic group and verbal learning and memory, our results suggest that the sex advantage of women in verbal learning and memory is equally present in ARMS as in FEP and HC individuals. As previous studies did not compare ARMS with HC and FEP individuals, this has not been demonstrated previously. Unexpectedly, we found that men had a shorter reaction time in the 2-back task than women independent of diagnostic group. This could indicate that men have a superior working memory performance since they responded faster during the target trials, while maintaining a comparable overall performance level. This result cannot be better explained by a generally enhanced processing speed as no sex differences in reaction time during CPT and Go/NoGo were detected. Our finding of a significant sex × group interaction in verbal IQ is difficult to explain as it is not substantiated by the literature. One potential explanation for a worse performance of women in the ARMS and FEP group could be that women in our sample have more severe positive symptoms than men as indicated by the BPRS psychosis/thought disturbance dimension score. However, an association between positive symptoms and verbal IQ has not been established in the literature and only appears to exist for negative and disorganised symptom dimensions [64, 65].

Some earlier studies [33, 66], which did not detect any sex differences in cognitive functioning were conducted in chronic schizophrenia patients who were seriously impaired and therefore represented a different patient population. It is conceivable that sex differences at a very low level of functioning do not exist or that they could not be detected because of floor effects. In the present study, we included mainly antipsychotic naïve ARMS and FEP individuals and therefore it should be noticed that our sample is not comparable to chronic schizophrenia patients. The following limitations should be taken into account: Our neuropsychological tasks were originally selected to assess the risk of psychosis and not specifically to detect sex differences. Therefore, our test battery did not include some of the most sensitive tasks to detect sex differences such as visuo-spatial or mental rotation tasks. Furthermore, meta-analyses suggest that sex-related cognitive performance differences are rather small [61]. Hence, our modest sample size could have precluded the detection of some sex effects. Another important aspect to consider is the conceptual difference of gender and sex. While gender refers to masculinity/femininity rooted in sociocultural descriptions (measured by a questionnaire), sex is a biologically reduced and dichotomous term. Lewine et al. [67] reported results that indicate stronger gender than sex effects. Accordingly, in this paper we used the term sex because we did not evaluate gender. Finally, it should be noted that neuropsychological performance in women has been shown to fluctuate with their monthly cycle [68-71] which we did not control in this study. High levels of ovarian hormones in the midluteal phase may facilitate certain skills that show a female advantage, while being detrimental to skills that normally show a male advantage [69]. Thus, it is possible that some effects would have been more pronounced if we had measured women at a specific point during their monthly cycle.

Taken together, our results suggest that sex differences in cognitive functioning in ARMS and FEP patients are not different from those seen in HC. Specifically, the female advantage in verbal learning and memory which has frequently been found in HC seems equally present in ARMS and FEP patients. Future studies should also consider menstrual status in women

as well as making a distinction between gender and sex to identify potential differences in cognitive functioning.

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All authors declare not to have any conflicts of interest that might be interpreted as influencing the content of the manuscript.

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Conflict of Interest

The authors declare that they have no conflicts of interest concerning this article.

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Table 1: Sample description

	Total group				ARMS			FEP			HC		
	Men N=174	Women N=118	p-value	N	Men N=73	Women N=45	p-value	Men N=56	Women N=32	p-value	Men N=45	Women N=41	p-value
Age	26.2 (6.67)	27.7 (8.92)	0.133	292	25.6 (6.36)	27.2 (9.67)	0.326	29.2 (7.35)	30.3 (10.4)	0.579	23.6 (4.77)	26.2 (6.22)	0.038*
Years of education	11.7 (2.99)	12.1 (3.04)	0.316	292	11.8 (3.04)	11.8 (3.00)	0.997	11.3 (3.08)	11.4 (3.12)	0.826	12.3 (2.74)	13.0 (2.87)	0.244
Antipsychotics currently:			0.989	290			0.150			0.770			1.000
no	148 (85.5%)	101 (86.3%)			70 (95.9%)	39 (88.6%)		33 (60.0%)	21 (65.6%)		45 (100%)	41 (100%)	
yes	25 (14.5%)	16 (13.7%)			3 (4.11%)	5 (11.4%)		22 (40.0%)	11 (34.4%)		0 (0.00%)	0 (0.00%)	
Chlorpromazine equivalent dose [mg]	221 (179)	204 (141)	0.735	40	217 (76.4)	245 (155)	0.742	222 (190)	185 (138)	0.538	.	.	
Antipsychotics compound:			0.123	290			0.198			0.124			1.000
none	148 (85.5%)	101 (86.3%)			70 (95.9%)	39 (88.6%)		33 (60.0%)	21 (65.6%)		45 (100%)	41 (100%)	
Aripiprazole	0 (0.00%)	2 (1.71%)			0 (0.00%)	0 (0.00%)		0 (0.00%)	2 (6.25%)		0 (0.00%)	0 (0.00%)	
Risperidone	6 (3.47%)	8 (6.84%)			1 (1.37%)	3 (6.82%)		5 (9.09%)	5 (15.6%)		0 (0.00%)	0 (0.00%)	
Quetiapine	6 (3.47%)	2 (1.71%)			0 (0.00%)	0 (0.00%)		6 (10.9%)	2 (6.25%)		0 (0.00%)	0 (0.00%)	
Olanzapine	13 (7.51%)	4 (3.42%)			2 (2.74%)	2 (4.55%)		11 (20.0%)	2 (6.25%)		0 (0.00%)	0 (0.00%)	
Antidepressants currently:			0.692	290			0.854			0.694			1.000
no	139 (80.3%)	97 (82.9%)			49 (67.1%)	28 (63.6%)		45 (81.8%)	28 (87.5%)		45 (100%)	41 (100%)	
yes	34 (19.7%)	20 (17.1%)			24 (32.9%)	16 (36.4%)		10 (18.2%)	4 (12.5%)		0 (0.00%)	0 (0.00%)	
Tranquilizer currently:			0.525	290			0.242			0.835			1.000
no	148 (85.5%)	96 (82.1%)			61 (83.6%)	32 (72.7%)		42 (76.4%)	23 (71.9%)		45 (100%)	41 (100%)	
yes	25 (14.5%)	21 (17.9%)			12 (16.4%)	12 (27.3%)		13 (23.6%)	9 (28.1%)		0 (0.00%)	0 (0.00%)	
BPRS total score	43.2 (11.7)	45.7 (12.7)	0.191	175	38.7 (9.57)	41.0 (10.7)	0.265	50.0 (11.4)	52.2 (12.6)	0.449	.	.	
BPRS Psychosis/Thought Disturbance	7.85 (3.64)	9.10 (4.21)	0.045*	178	5.92 (2.29)	6.93 (3.02)	0.072	10.8 (3.33)	12.3 (3.67)	0.093	.	.	
SANS total score	24.8 (16.3)	21.2 (15.7)	0.166	155	25.3 (17.6)	18.9 (16.3)	0.084	24.2 (14.8)	24.2 (14.7)	0.992	.	.	

ARMS = at-risk mental state; FEP = first episode psychosis; HC = healthy controls; BPRS = Brief psychiatric rating scale; SANS = Scale for the assessment of negative symptoms; * $p < 0.05$

Regarding psychopathological measures (BPRS and SANS) the total group consists of ARMS + FEP (without the HC's); continuous variables are described by means and standard deviation in brackets

Table 2: *P*-values of ANCOVAs with ARMS, FEP and HC

	uncorrected			corrected		
	group	sex	group x sex	group	sex	group x sex
IQ						
Nonverbal IQ	<0.001***	0.516	0.797	0.002**	0.777	0.945
Verbal IQ	0.014	0.308	0.028*	0.033*	0.665	0.739
Executive Functions						
ToH total time	0.006**	0.192	0.650	0.016*	0.665	0.945
ToH 4 and 5 disc moves	0.015*	0.344	0.916	0.034*	0.665	0.945
WCS total assignments	0.002**	0.496	0.921	0.011*	0.777	0.945
WCS perseveration score	0.059	0.272	0.558	0.101	0.665	0.945
Go/NoGo reaction time	0.003**	0.530	0.634	0.013	0.777	0.945
Go/NoGo c (response bias)	0.238	0.580	0.505	0.310	0.777	0.945
Go/NoGo d' (sensitivity)	0.170	0.877	0.763	0.237	0.908	0.945
Attention & Working Memory						
WM reaction time	<0.001***	0.046*	0.639	<0.001***	0.413	0.945
WM c (response bias)	0.005**	0.358	0.103	0.015*	0.665	0.945
WM d' (sensitivity)	0.001**	0.239	0.290	0.008**	0.665	0.945
CPT reaction time	0.004**	0.212	0.821	0.013*	0.665	0.945
CPT slowing	0.173	0.141	0.913	0.237	0.665	0.945
CPT c (response bias)	0.061	0.627	0.334	0.101	0.777	0.945
CPT d' (sensitivity)	0.019*	0.326	0.410	0.038*	0.665	0.945
Verbal learning & Memory						
CVLT total correct trial 1-5	0.012*	0.046*	0.938	0.031*	0.413	0.945
CVLT long delay free recall	0.062	0.098	0.859	0.101	0.634	0.945
CVLT Semantic cluster ratio	0.267	0.241	0.624	0.316	0.665	0.945
CVLT Serial cluster ratio	0.324	0.522	0.279	0.367	0.777	0.945
CVLT Percent primacy recall	0.746	0.636	0.660	0.775	0.777	0.945
CVLT Percent middle recall	0.256	0.716	0.767	0.316	0.810	0.945
CVLT Percent recency recall	0.579	0.908	0.945	0.627	0.908	0.945
CVLT proactive interference	0.101	0.870	0.890	0.155	0.908	0.945
CVLT retroactive interference	0.920	0.048*	0.362	0.920	0.413	0.945
Composite						
Total score	<0.001***	0.658	0.886	<0.001***	0.777	0.945

ARMS = at-risk mental state; FEP = first episode psychosis; HC = healthy controls; ToH = Tower of Hanoi; WCS = Wisconsin Card Sorting Test; CPT = Continuous performance Task; CVLT = California Verbal Learning Task; * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

Figure Legend

Figure 1. Cognitive performance of women compared to men in at-risk mental state (ARMS) for psychosis individuals, first episode psychosis (FEP) patients, healthy controls (HC) and in the total group. The dotted horizontal line at zero represents the performance of men. Differences are expressed in units of Cohen's d and are significant if the 95% confidence interval (vertical line) does not overlap with zero. Variables with a minus sign were reversed so that positive scores always represent good performance. Differences are adjusted for the influence of age, years of education and use of antipsychotics. In the total group, we additionally corrected for diagnostic group.
ARMS = at risk mental state; FEP = First episode psychosis; HC = Healty controls; total = ARMS +FEP + HC; ToH = Tower of Hanoi; WCS = Wisconsin Card Sorting Test; CPT = Continuous performance Task; CVLT = California Verbal Learning Task.