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Investigation of sex differences in delusion-associated cognitive biases

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A B S T R A C T

In the past few decades, sex differences have been identified in a number of clinical, cognitive and functional outcomes in patients with schizophrenia spectrum disorders. However, to date, sex differences in higher-order cognitive biases have not been systematically studied. The present study aimed to examine sex differences in jumping-to-conclusions and evidence integration impairment based on data collected in two previous studies in patients with schizophrenia spectrum disorders and healthy controls. For this purpose, data from $n = 58$ patients and $n = 60$ healthy controls on the Fish Task (as a measure of jumping to conclusions) and bias against disconfirmatory evidence (BADE; as a measure of evidence integration) task were analyzed. Results indicated a lack of sex differences in jumping-to-conclusions and evidence integration impairment both in patients with schizophrenia spectrum disorders and healthy controls. Although the present study was adequately powered to detect sex differences of a low medium effect size, larger studies are warranted to exclude differences of a smaller magnitude between men and women regarding delusion-associated cognitive biases.

1. Introduction

As far back as 1919, Kraepelin observed that males were more frequently afflicted by `dementia praecox´ than females (Kraepelin, 1971). Research conducted in the following decades has unveiled a multitude of other sex differences in schizophrenia spectrum disorders, and the importance of gender-sensitive research in the field of psychosis has been stressed (Riecher-Rössler and Häfner, 2000). A number of review papers (Abel et al., 2010; Leung and Psych, 2000; Ochoa et al., 2012) have highlighted robust sex differences in schizophrenia spectrum disorders regarding incidence rates (higher in men; Abel et al., 2010; Ochoa et al., 2012) and age at onset of the illness (higher in women; Leung and Psych, 2000; Ochoa et al., 2012). Sex differences regarding symptom profiles are less consistent, with some (but not all) studies reporting more frequent negative symptoms in men, whereas affective symptoms seem to be more frequently present in women (Leung and Psych, 2000; Ochoa et al., 2012; Roth, 2008). Regarding illness course, it has been noted that young women tend to have higher remission rates and lower relapse rates than same-aged men; however, as women get older, the course of the illness tends to worsen compared to men (Leung and Psych, 2000; Ochoa et al., 2012). Sex differences have been also reported in terms of cognitive function, with female patients outperforming male patients in several cognitive domains such as attention, language, memory and executive function (Bozikas et al., 2010; Goldstein et al., 1998), although these findings have not always been replicated (Goldberg et al., 1995; Moriarty et al., 2001). Finally, women exhibit better premorbid and social functioning and lower rates of substance abuse than men (Leung and Psych, 2000; Ochoa et al., 2012; Roth, 2008). Although psychosocial factors have been implicated in the above sex differences, the greatest weight of the evidence leans towards a biological account, in particular towards hormonal differences and the role of estrogen in women (Riecher-Rössler, 2017).

A recent active research field in schizophrenia concerns higher-order abnormalities in belief generation and evaluation processes, which are called “cognitive biases” and are thought to contribute to the emergence and maintenance of delusions (Garety and Freeman, 2013; Moritz et al., 2017). The most studied cognitive bias in schizophrenia is jumping-to-conclusions (JTC), which reflects a tendency of patients with schizophrenia to draw firm conclusions based on very little evidence (Dudley et al., 2016). A second prominent cognitive bias in schizophrenia reflects a tendency of patients to hold on to an opinion or attitude even in the light of compelling counterarguments or proof of the contrary; it has been consistently demonstrated that people with schizophrenia manifest an impaired ability to integrate disconfirmatory or disambiguating information (also referred to as bias against disconfirmatory evidence (BADE); Woodward et al., 2006).

To the best of our knowledge, the question whether sex differences exist for delusion-related cognitive biases has been scarcely

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investigated so far. Although these biases are mainly linked to delusion severity (McLean et al., 2017), which does not appear to be affected by sex (Leung and Psych, 2000; Ochoa et al., 2012; Roth, 2008), one might still expect differences between male and female patients because of the association of cognitive biases with factors such as level of functioning (Andreou et al., 2014b), neurocognitive performance (Andreou et al., 2015a; Freeman et al., 2014; Garety et al., 2013; Moritz et al., 2014) and dopaminergic activity (Andreou et al., 2014a; Andreou et al., 2015b).

In the only existing study reporting cognitive bias performance according to sex, González et al. (2018) reported no sex differences in JTC in patients with recent-onset psychotic disorders. However, these authors used a dichotomous definition of JTC, which may have reduced the power to detect subtle differences in the amount of evidence gathering between men and women. Moreover, it would be interesting to assess different cognitive biases with respect to a postulated role of sex in dopaminergic accounts of psychotic symptoms: It has recently been suggested that dopaminergic activity may differ between males and females due to circulating estrogens in women (Riecher-Rössler, 2017). Hence, one might expect to observe significant sex differences in BADE but not JTC, since previous studies have shown that antipsychotic medication in patients and subtle dopaminergic modulations in healthy controls affect the former (Andreou et al., 2015b), but not the latter bias (Andreou et al., 2015b, 2014a; Ermakova et al., 2014; Menon et al., 2008).

The present study aimed to explore potential sex differences in JTC and BADE in patients with schizophrenia spectrum disorders; we also assessed a healthy control group in order to exclude antipsychotic medication as the sole cause of observed effects, or lack thereof. Given the above considerations, we tentatively expected to find reduced BADE in women compared to men, but no sex differences in JTC. However, given the lack of previous research, we did not formulate any strong hypotheses regarding the presence and direction of differences in cognitive biases.

2. Methods

2.1. Participants

Data from healthy participants and patients with schizophrenia spectrum disorders from two previous studies (Andreou et al., 2014a; Moritz et al., 2013) were used for the present analysis. Healthy participants originated from a placebo-controlled study investigating the effects of a dopaminergic agonist and dopaminergic antagonist on delusion-related reasoning biases (Andreou et al., 2014a), and from an unpublished healthy control dataset collected in the context of a clinical trial (Moritz et al., 2013). In both studies, healthy individuals were recruited among university students and from the community. In order to be eligible for study participation, healthy participants were required to be between 18 and 60 years of age, be right handed, and have sufficient proficiency in the German language. Exclusion criteria were any past or present psychiatric or neurological disorder; a first-degree relative with a history of schizophrenia or bipolar disorder; history of craniocerebral trauma, arterial hypertension, or any other cardiological or serious medical conditions; pregnancy; or treatment with any psychotropic or other drugs. One of the studies (Andreou et al., 2014a) included drug-challenge with dopaminergic drugs; only data pertaining to the placebo condition from this study were used in the present analysis.

The patient sample stemmed from a study investigating the efficacy of group Metacognitive Training (MCT) on delusion-associated cognitive biases (Moritz et al., 2013). Participants were in- and outpatients with a DSM-IV diagnosis of a schizophrenia spectrum disorder. In order to be included in the study, participants were required to be between 18 and 65 years of age, and have current or past delusions. Participants were excluded from the study if they fulfilled DSM-IV criteria for substance dependence, if they had an IQ < 70, or if they scored 5 or higher on the PANSS hostility item and 6 or 7 on the PANSS paranoia/suspiciousness item. Only data from baseline assessments were used for present analyses.

The two samples differed in age and sex distribution. Patients were significantly older than healthy controls ($M = 35.34$ years (11.04) vs. $M = 28.28$ years (9.36), t (135.34) $= 4.52$, $p < 0.001$), and the sex distribution was unequal across samples ($n = 32$ males vs. $n = 28$ females in the healthy sample, compared to $n = 76$ males vs. $n = 28$ females in the patient sample). To make the two samples comparable and increase homogeneity in the merged sample that we used for analyses, we excluded all patients older than 40 years and a random subsample ($n = 30$) of male patients from the present analyses using a built-in function in SPSS.

2.2. Outcomes

2.2.1. Psychopathological assessment

The MINI-International Neuropsychiatric Interview (MINI; Sheehan et al., 1998) was used to confirm diagnoses of schizophrenia spectrum disorders in the patient sample. Data on the psychometric properties of the MINI suggest good validity and reliability of the instrument (Sheehan et al., 1998). Severity of psychotic symptoms was assessed using the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1989). Results on the psychometric properties of the PANSS support the scale's validity and reliability (Kay et al., 1988). In the present study, five PANSS factors (positive, negative, disorganization, excitement, distress) were calculated (van der Gaag et al., 2006).

2.2.2. Fish task

Data gathering and jumping to conclusions were assessed with the Fish Task (Moritz et al., 2010). Participants were shown two lakes containing orange and grey fish, lake A with 80% orange and 20% grey fish, and lake B with the reverse ratio. Ten fish were successively presented; following each draw, participants were asked to indicate whether they had arrived at a decision regarding the origin of the fish (and, if so, which lake it came from); unknown to the participants, the sequence was predetermined (O—O—O—G—O—O—O—O—G—O). All fish drawn remained visible throughout the task in order to minimize working memory demands. The variables of interest for this study were (a) the number of draws until the participant reached a decision regarding the origin of the fish (i.e., draws to decision), and (b) the probability estimate (on a 100-point scale) at which this decision was made (i.e., decision threshold). For both parameters a higher number reflects more cautious inference-making. Jumping-to-conclusions (JTC) was defined as decisions made about the origin of the fish after presentation of 1 or 2 fish only.

2.2.3. BADE task

The bias against disconfirmatory evidence (BADE) task (Veckenstedt et al., 2011; adapted from Woodward et al., 2007) involves presentation of initially ambiguous scenarios that are gradually disambiguated. Each trial begins with an ambiguous statement, followed by two further statements that provide disambiguating information. Four possible interpretations are provided for the scenario (the true interpretation, one absurd and two plausible lures). After each statement, the participant is required to provide probability ratings for each of the four interpretations on a visual analogue scale from 0 to 10 and indicate whether they have reached a decision regarding the true interpretation. The task includes 16 experimental trials, in which the initial statement favors one of the lure interpretations, while the two following statements gradually deliver evidence for the true interpretation. Eight further control items, in which the true interpretation is from the beginning the most plausible one, are included to mask the rationale of the paradigm and are not considered in the analyses. For the present analysis, we followed the scoring procedure proposed by

Table 1
Sample characteristics.

	Patients with schizophrenia spectrum disorders (n = 58)				Healthy control group (n = 60)			
	Men (n = 33)		**Women (n = 25)**		**Men (n = 32)**		**Women (n = 28)**	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Age (years)	30.30	5.48	31.96	6.35	26.97	5.67	29.79	12.26
	Mean	**SD**	**Mean**	**SD**				
Psychiatric admissions	4.09	5.76	3.28	3.90				
PANSS scores								
P1 (delusions)	2.42	1.66	2.36	1.44				
PANSS positive symptoms	14.75	7.20	13.20	4.95				
PANSS negative symptoms	14.45	6.24	13.60	4.03				
PANSS disorganization	15.18	5.55	14.00	4.49				
PANSS excitement	12.85	3.86	12.08	3.20				
PANSS emotional distress	17.70	6.64	16.04	4.42				
PANSS total	53.94	15.29	49.92	10.04				
Antipsychotic medication dose (chlorpromazine equivalents)	829.17	400.38	799.11	725.89				
	n	**%**	***n***	**%**				
Education								
High-school diploma	19	57.6%	15	60.0%				
Junior high-school diploma	9	27.3%	6	24.0%				
General equivalency diploma	4	12.1%	3	12.0%				
No diploma	1	3.0%	1	4.0%				

PANSS: Positive and Negative Syndrome Scale

Bronstein and Cannon (2018) which calculates two variables based on factor analyses of BADE performance: (a) 'evidence integration impairment', corresponding to the ability to use disambiguating evidence to update beliefs, and (b) 'conservatism' or 'positive response bias', which reflects reluctance to provide high plausibility ratings for statements supported by evidence (Bronstein and Cannon, 2018; Sanford et al., 2014). Of the two variables, only evidence integration impairment has been associated with delusion propensity (Bronstein and Cannon, 2018; Sanford et al., 2014) and was a variable of interest in the present study; however, positive response bias was also included in analyses for the sake of completeness.

2.3. Statistical analyses

Data were analyzed using SPSS Statistics Version 24.0 (IBM Corp. Released 2017, Armonk, NY). Analysis of Variance (ANOVA), independent samples *t*-test, and Pearson's chi-square were utilized to verify that the four groups (men with schizophrenia spectrum disorders, women with schizophrenia spectrum disorders, healthy male controls, and healthy female controls) did not differ on any demographic and clinical characteristics.

Continuous variables pertaining to the Fish Task were investigated using a 2 (group: patients and healthy controls) × 2 (sex: male and female) Multivariate ANOVA (MANOVA), with group and sex as between-subjects factors, and draws to decision and decision threshold as dependent variables. Main effects of group and sex, as well as group × sex interactions were assessed in the analysis. Significant effects were followed-up with separate ANOVAs for each dependent variable with Bonferroni correction for multiple testing. Log-linear analysis was used to investigate data pertaining to dichotomous variable JTC. Group (patient and healthy controls), sex (male and female) and JTC (presence and absence) were entered as variables in the model. Significant effects were followed-up using chi-square tests.

Data relating to the BADE task was analyzed using a two-way Multivariate Analysis of Variance (MANOVA) with Evidence Integration Impairment (EII) and Positive Response Bias (PRB) as dependent variables, and Group and Sex as fixed factors. Significant effects were followed-up with separate ANOVAs for each dependent variable with Bonferroni correction for multiple testing. All tests of significance in the analyses were two-tailed and the level of significance applied was 0.05.

3. Results

A total of 60 healthy subjects and 58 patients with schizophrenia spectrum disorders were included in the analysis. The majority of patients had a diagnosis of schizophrenia (n = 42); other diagnoses were schizoaffective disorder (n = 10), brief psychotic disorder (n = 4) and schizophreniform disorder (n = 2).

Preliminary analysis of the sample characteristics revealed no significant differences in sex distributions between patients and healthy controls [χ^2 (1) = 0.15, p = 0.715]. Patients were trend-wise older than healthy controls [F(1,114) = 3.609, p = 0.06], but neither the main effect of sex [F(1,114) = 2.380, p = 0.12] nor the sex × group interaction [F(1,114) = 0.160, p = 0.69] reached significance.

There was no significant difference among male and female patients with schizophrenia spectrum disorders regarding the level of education attained [χ^2 (3) = 0.11, p = 0.990]. No data were collected regarding level of education in healthy subjects, which is why group differences in this variable could not be assessed. Regarding clinical characteristics, there was no significant difference among male and female patients with regard to the number of psychiatric admissions [t (56) = 0.61, p = 0.502], PANSS P1 (delusions) scores [t (56) = 0.154, p = 0.878], PANSS total score [t (55.024) = 1.21, p = 0.233], nor any of the five PANSS factors (i.e., positive symptoms, negative symptoms, disorganization, excitement, and emotional distress; van der Gaag et al., 2006; all p's > 0.2) or antipsychotic medication dose [t(54) = 0.198, p = 0.844]. Table 1 provides summary statistics of demographic and clinical characteristics for both the patient and the healthy control sample.

Table 2 provides descriptives of cognitive bias indices per participant group and sex. Regarding the analysis of draws to decision and decision threshold, the MANOVA revealed no significant main effect of sex [F (2, 104) = 0.66, p = 0.520, η^2p = 0.012] nor a significant group × sex interaction [F (2, 104) = 0.01, p = 0.990, η^2_p = 0.000]. A significant main effect of group was observed [F (2, 104) = 9.79, p < 0.001, η^2_p = 0.158]. Separate follow-up ANOVAs revealed a significant difference in draws to decision between patients with schizophrenia spectrum disorders and healthy controls [F (1, 105) = 19.76, p < 0.001, η^2p = 0.158; mean difference controls vs. patients: 2.16, 95% CI: 1.20–3.12]. The effect remained significant after applying the Bonferroni correction. Decision threshold was not different between patients and healthy controls [F (1, 105) = 0.43, p = 0.511, η^2p = 0.004].

Table 2
Fish Task and BADE scores for men and women separately in the two participant groups.

	Patients with schizophrenia spectrum disorders (n = 58)				Healthy control group (n = 60)			
	Men (n = 33)		**Women (n = 25)**		**Men (n = 32)**		**Women (n = 28)**	
	n	**%**	***n***	**%**	***n***	**%**	***n***	**%**
Fish task: presence of JTC	15	45.5%	13	52.0%	8	25.0%	7	25.0%
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Fish task: draws to decision	2.91	2.17	3.20	2.80	5.22	3.13	5.86	3.55
Fish task: decision threshold	77.49	24.18	80.68	17.27	80.11	12.99	82.57	10.47
BADE task: evidence integration impairment	3.05	2.11	3.31	1.94	2.58	1.55	2.20	1.06
BADE task: positive response bias	8.23	3.69	9.72	3.40	8.87	2.86	8.98	3.11

JTC: Jumping to conclusions (categorically defined as reaching a conclusion after a maximum of 2 beads); BADE: Bias against disconfirmatory evidence

No sex effects were observed regarding the JTC effect. The three-way log-linear analyses produced a final model that retained the two-way interaction group × JTC [χ^2 (1) = 6.98, p = 0.008]. To break down this effect, a Pearson's chi-square test was performed on the group and JTC variables. JTC rates differed significantly between the two groups [χ^2 (1) = 6.90, p = 0.009], as only 25% of healthy controls but 48% of patients showed a JTC response style (odds ratio 2.8).

Regarding BADE variables, the main effect of sex was non-significant [F (2,113) = 1.10, p = 0.337, η^2p = 0.019], as was the interaction group × sex [F (2,113) = 0.86, p = 0.428, η^2p = 0.015]. The main effect of group was found to be significant [F (2,113) = 3.34, p = 0.039, η^2p = 0.056]. Univariate tests revealed a significant group difference in evidence integration impairment [F (1,114) = 6.04, p = 0.016, η^2p = 0.050] with a mean difference of 0.78 between healthy controls and patients (95% CI: −1.41 to −1.15). The group difference in positive response bias was not found to be significant [F (1,114) = 0.01, p = 0.937, η^2p = 0.000].

3.1. Additional analyses

Given the negative results, we conducted further analyses to determine whether a lack of power might have prevented us from detecting sex differences in cognitive biases. A sensitivity analysis conducted in G*power (Faul et al., 2007) indicated that our sample size was sufficient to detect an effect size in the low medium range (Cohen's d = 0.523) with error probability of 0.05 and 80% power.

Sex differences in cognitive biases could, however, be expected to be of a smaller effect size than those reported between patients with delusions and healthy controls. Therefore, we applied an equivalence testing procedure, the 'two one-sided tests' (TOST) procedure (Schuirmann, 1987), to estimate whether the observed lack of sex differences in the present study were likely to result from a lack of statistical power, or instead from a genuine absence of an effect of a meaningful size. TOST specifies equivalence bounds based on the smallest effect size of interest (SESOI); results significantly falling within these equivalence bounds are taken to be equivalent to the absence of a meaningful effect (Lakens, 2017). For the present analysis, we selected an arbitrary SESOI as d = 0.3, which would correspond to a mean difference of 0.96 draws to decision and 5.2% in the probability threshold for decisions in the Fish Task, and a difference of 0.5 in evidence integration impairment and 0.98 in positive response bias in the BADE Task.

The TOST procedure based on Student's t-test could confirm statistical non-inferiority of men vs. women for evidence integration impairment [t(116) = 1.930, p = 0.03] and for women vs. men for draws to decision [t(116) = 2.560, p = 0.006], decision threshold [t (116) = 2.523, p = 0.007] and positive response bias [t(116) = 2.909, p = 0.002], indicating a genuine lack of differences in the respective directions. However, the results of one-sided t-tests regarding statistical non-inferiority of women vs. men for evidence integration impairment [t (116) = 1.312, p = 0.116], and for men vs. women for the other variables were not significant [Fish Task draws to decision: t (116) = 0.682, p = 0.248; decision threshold: t(116) = 0.719, p = 0.237; BADE positive response bias t(116) = 0.333, p = 0.370]. Thus, the possibility cannot be excluded that a lack of power may have prevented us from detecting reduced evidence integration impairment, more cautious evidence gathering and increased positive response bias in women compared to men.

4. Discussion

The present study aimed to explore sex differences in JTC and BADE among patients with schizophrenia spectrum disorders and healthy controls. Group effects observed were in the direction reported in previous studies (McLean et al., 2017), i.e., reduced draws to decision and increased rates of JTC and evidence integration impairment in patients compared to healthy controls. Regardless of participant group, men and women required a similar amount of evidence to arrive at a decision, reached decisions at similar subjective probability levels, and showed similar rates of a JTC response style. Moreover, across groups, male and female participants evidenced similar evidence integration.

The above findings argue against the existence of sex differences in JTC and evidence integration both in patients with schizophrenia spectrum disorders and in healthy controls. Our results with respect to JTC are consistent with those of a recent study that found similar rates of JTC in male and female patients with recent-onset psychosis (González et al., 2018). In conjunction with the finding of a recent meta-analysis that JTC and BADE are associated with delusional severity (McLean et al., 2017), the lack of a difference between male and female patients might be explained by the lack of sex differences in delusion severity in the present sample, or in previous psychopathological studies in patients with psychotic disorders (Leung and Psych, 2000; Ochoa et al., 2012; Roth, 2008).

Our study was adequately powered to detect differences in cognitive biases between men and women at an effect size in the low medium range, which is lower than the effect size reported for comparisons of patients with schizophrenia and current delusions with healthy controls, or with psychiatric patients without delusions (d = 0.56–0.84) in a recent meta-analysis (McLean et al., 2017). However, it is likely that sex differences in cognitive biases, if present, might represent a subtler effect, in the small effect size range.

Based on additional equivalence tests, we could not exclude the possibility that women might show reduced evidence integration impairment, more cautious evidence gathering and increased positive response bias compared to men, at a small effect size. Regarding jumping-to-conclusions, sex differences in the observed direction would be consistent with previous reports of better cognitive functioning (Bozikas et al., 2010; Goldstein et al., 1998) and functional outcomes (Leung and Psych, 2000; Ochoa et al., 2012; Roth, 2008), in female patients with psychotic disorders, both of which have been associated with this cognitive bias (Andreou et al., 2015a, 2014b; Freeman et al., 2014; Garety et al., 2013; González et al., 2018; Moritz et al., 2014; Ochoa et al., 2014). However, it should be noted that positive response bias, a bias not associated with delusions, also showed differences

between men and women in the present study. Thus, at this point, it is uncertain if the observed (small) sex differences in cognitive biases are specific to their delusion-associated aspects. Rather, they may be reflective of general differences between men and women in decision making, which have associated with a number of diverse factors such as self-confidence (Cross et al., 2017), sensitivity to short-term loss/punishment (Alarcón et al., 2017; Ding et al., 2017; van den Bos et al., 2013) or influence by stress (Kluen et al., 2017), and implicate both emotional and cognitive control systems (van den Bos et al., 2013). Further studies in larger samples are warranted to ascertain the presence of subtle sex differences in delusion-associated cognitive biases, and their exact nature.

A number of limitations of the study should be discussed. First of all, one should take into consideration that healthy controls and patients originated from two different studies. Although we tried to match the two samples in order to make the mixed sample as homogeneous as possible regarding key sociodemographic variables such as age and sex, there may have been differences in other variables between patients and controls. Important in this regard is the fact that information on the level of education of healthy controls was lacking. This is of particular significance as it has been evidenced that JTC is associated with general intelligence (IQ) in patients with first-episode psychosis and healthy controls (Falcone et al., 2015). On a similar note, no data on subjects' neuropsychological test performance was available. This may have been of importance as evidence gathering has been found to be dependent upon neurocognitive functioning (Andreou et al., 2015a; Freeman et al., 2014; Garety et al., 2013; González et al., 2018; Ochoa et al., 2014). Finally, both samples consisted mainly of young people, which limits the generalizability of results to older individuals, a fact which should be taken into account in future studies.

In summary, the current study could find no sex differences in JTC and evidence integration impairment in patients with schizophrenia spectrum disorders. Although the present study was adequately powered to detect sex differences of a low medium effect size, further studies are warranted to exclude differences of a smaller magnitude between men and women regarding delusion-associated cognitive biases.

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