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Sex versus Gender Differences in Schizophrenia: The Case for Normal Personality Differences

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Introduction

As recently pointed out by Silverstein et al (2014) “... despite thousands of new studies every year, and major technological advances, schizophrenia research is not leading to consistent improvements in the lives of people with the disorder” (p. 259). One of the obstacles identified in trying to advance treatment is within schizophrenia heterogeneity, a phenomenon that has plagued the study, understanding, and treatment of schizophrenia since the time of Kraepelin and Bleuler. Numerous efforts over three decades have been made to understand this variability within schizophrenia; these include the study of sociodemographic characteristics, subtypes, premorbid competence, genetic risk, familial environment, and brain morphology (Corvin et al, 2013; Johnston, 1982; Silveira et al, 2012). We suggest in this study the use of personality differences, using gender as an exemplar and proof of concept, to address some of the variability in the clinical expression in schizophrenia.

The study of personality in schizophrenia has exclusively focused on between-diagnosis comparisons in the pursuit of identifying diagnostic markers, with the assumption that there are shared personality characteristics in schizophrenia (Berenbaum & Fujita, 1994; Ohi et al, 2016). There is a strong bias, introduced by Kraepelin and Bleuler, that the pre-psychosis personalities of schizophrenia patients are different from those with other disorders or healthy individuals. In a meta-analysis of the then-current research, Berenbaum & Fujita (1994) went so far as to ignore the absence of statistical significance in their findings to interpret the data as supporting personality differences in pre-schizophrenia individuals. Current research, while more rigorous in adhering to statistical guidelines, continues to focus on the “unique” personality characteristics of schizophrenia (Ohi et al, 2016).

The study of sex differences in schizophrenia has yielded promising findings, largely in the realm of timing of disorder as a function of neurohormonal processes (e.g. Abel et al, 2010; Goldstein & Lewine, 2000; Salem & Kring, 1998). With rare exceptions, however, “sex” and “gender” have been conflated both in the use of language and in conceptualization.

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Specifically, although personality may be embedded in the biology of the individual (see Canli, 2006), sex and gender are not the same. It has been more than two decades since Deaux (1993) called for clarification of the two terms. She argued that sex refers to the genetic features that identify man or woman, while gender incorporates aspects of personality, namely more masculine or more feminine, that can apply to either or both of the sexes. The personality framework of gender (semi-independent of sex) is exemplified in the work of Bem and the identification of androgynous, as well as feminine and masculine types across the sexes (Bem, 1994). Importantly, subsets of both men and women were classified as masculine, feminine, and androgynous. With respect to research strategies, Deaux (1993) captured this type of separation between sex and gender in pointing to the differences between “sex comparisons” [woman to man and girl to boy] and “gender comparisons” [gender identification, gender stereotypes, and gender roles]. The two types of comparisons can yield different results and may have different implications, a perspective we explore in understanding schizophrenia.

The purpose of this study was to contrast sex and gender differences in schizophrenia, viewing gender as a personality characteristic. In general, there are multiple confirmed “sex differences”, ranging across biological, psychological, and social domains and include age of onset of the disorder, incidence and prevalence of psychosis, risk factors, symptom expression and outcome (Abel et al, 2010; Falkenburg & Tracy, 2012; Goldstein & Lewine, 2000; Nasser et al al, 2002). Briefly, the data suggest that men with schizophrenia have an earlier onset of psychosis, greater social impairments, more negative symptoms, poorer neuropsychological functioning, and poorer outcomes than women with schizophrenia. The focus of this study is the symptomatic expression of affect. Specifically, women are more likely than men to exhibit affect, in particular negative affect such as depression and anxiety, than are men. All of the studies reported in published reviews of sex differences used self-identified sex (woman/man comparisons) as the independent variable, although just as often as not using the term “gender” to refer to the man-woman categorization. In short, none of these studies distinguished between sex and gender, thereby overlooking potential sex, gender (personality), or sex by gender interactions.

As we reported earlier (Lewine 1994; 2004), consideration of sex and gender separately yielded provocative findings in a large sample of schizophrenia patients. Although among those with schizophrenia, women tended to do better than men on tests of neuropsychological functioning, feminine (as measured by the MMPI mf scale) of *both* sexes performed better than masculine individuals of *both* sexes. The current study examined the separate impacts of sex and gender on the clinical expression of schizophrenia, with a particular focus on depression for which there is a well-established sex difference. If sex and gender are, indeed, not synonymous with one another, we would expect them to have different relationships with well-established “sex” differences or to account for what appear to be sex differences. A better understanding of personality characteristics (measured as gender in this study), in contrast to sex, could have significant implications for our diagnosis, treatment, and understanding of schizophrenia.

Methods

Participants

The data used in this study were collected as part of a larger study of sex differences in schizophrenia (details available from the first author). The data from 213 participants (141 men and 72 women) were used in this study. The majority of patients were diagnosed with schizophrenia ($n = 170$) and the remainder with schizoaffective disorder ($n = 43$). As expected, a significantly larger proportion of women (33.3%) than men (13.5%) received the diagnosis of schizoaffective disorder (Fisher's Exact Test, $p = .002$). A summary of participant demographic characteristics is provided in Table 1. Participants met the diagnostic criteria of schizophrenia according to the DSM-III-R. Trained clinicians conducted semi-structured interviews and completed clinical ratings; the patients completed self-report questionnaires, including the MMPI.

Measures

Gender-MMPI—We used the MMPI mf (masculine-feminine) scale to measure gender, a strategy supported by the literature (Nasser et al, 2002). Further, the mf scale has been reported to exhibit significant overlap with the Bem Sex Role Inventory and the Personal Attributes Questionnaire, both more widely accepted gender measures (Volentine, 1981). To make gender comparable to sex assignment in this study, namely dichotomous, following Bem's strategy we generated two categories of gender: masculine and feminine. The mf scale contains a total of sixty items covering four major content areas: interests in vocations and hobbies, aesthetic and religious preferences, activity-passivity, and personal sensitivity.

High scores reflect sex-atypical characteristics. An atypical male would be passive and socially sensitive, while the atypical female would be considered aggressive and dominating. Easy going and adventurous traits would represent the typical male role, while the typical female role would be represented by more submissive and passive traits. The mf scale was used to classify men and women as sex typical or atypical (T-scores above 60 relative to large non-clinical samples), yielding four groups: "masculine" men, "feminine" men, "masculine" women, and "feminine" women.

Of the 141 men, 74.4% were classified as sex atypical (feminine) and 21.7% of the 72 women were classified as sex atypical (masculine), the distributions approaching statistical significance (Fisher's Exact Test, $p = .055$). The differential distribution of gender atypical by sex is consistently reported in the study of both patients and healthy individuals (Duckworth & Anderson, 1986). That is, more men (especially among more educated) score in the atypical range than do women.

Clinical expression: (1) MMPI- patients completed the MMPI, from which profiles were generated, excluding the mf scale; (2) Hamilton Depression Rating Scale-clinician rating of depressive symptoms; (3) Scale for Assessment of Positive Symptoms [SAPS] and Scale for Assessment of Negative Symptoms [SANS]-clinician rated positive and negative symptoms; (4) Global Assessment of Functioning [GAF]-clinician rating of patient's social, vocational, and overall functional level.

Results

Sociodemographic characteristics

As expected from prior analyses of these data, men were significantly younger than women at age of first hospitalization for psychosis (Table 1; $F_{1, 207} = 5.639$, $p = .018$). Masculine patients were only slightly younger at first hospitalization than feminine patients (22.6 and 22.9, respectively, ns). The interaction of sex and gender was also not statistically significant.

Clinical presentation

MMPI (Figure 1 [Men] and 2 [Women]): We divided a conventional significance level of .05 by the 11 MMPI clinical scales, resulting in .0045 as the statistical cut point for considering significance in a MANOVA of all MMPI scales (excluding mf), using mf defined gender and self-reported sex as the independent variables. There were two highly significant main effects of Gender, in each case with feminine patients, independent of sex, scoring higher than masculine patients: depression ($F_{1, 209} = 8.678$, $p = .004$) and hysteria ($F_{1, 209} = 11.397$, $p = .001$). There were no significant sex differences and only one Sex X Gender interaction effect on MMPI scales: masculine women and feminine men scored significantly higher than their counterparts on the F scale ($F_{1, 209} = 13.420$, $p < .0001$, often interpreted as a sign of distress; that is, within each sex, the sex atypical group reported more distress. It is important to point out that there were no significant differences among the groups in Sc, the scale that measures psychosis severity.

We conducted a series of ANCOVAs examining the effect of Gender on depression, holding constant years of education, full scale IQ (WAIS), SES, age of first hospitalization, age at MMPI administration, and duration of illness at time of testing. None of the covariance analyses changed the highly significant effect of Gender on depression.

Women were rated higher on the Hamilton Depression Scale than men (11.2 vs 7.5, $F_{1, 112} = 2.090$, $p = .151$), while Feminine patients were rated higher than Masculine patients (9.7 vs 6.0; $F_{1, 112} = 1.812$, $p = .181$). Within sex, Feminine patients were rated as more depressed than Masculine patients for both men (8.3 vs 5.5, ns) and women (12.0 vs 8.5, ns). There were no significant main or interaction effects for the SAPS, the SANS, or the GAF.

In sum, the use of gender grouping yielded clear and strong evidence of differences between feminine and masculine schizophrenia patients, *independent of sex*, in affect expression, as reflected in depression and consistent with characteristics of hysteria, largely reflecting anxiety. The effect of gender on depression was not altered by a broad range of sociodemographic and clinical variables and was not accounted for by symptom or severity differences in schizophrenia as reflected in the MMPI Sc, clinician rated negative and positive symptoms of schizophrenia, or GAF scores. The clinician ratings of depression were consistent with the findings based on self-report (MMPI), although not at the same level of statistical significance.

Discussion

Gender clearly had a stronger association with self-reported depression than did sex. Feminine individuals, irrespective of sex, were significantly more depressed than were masculine patients. The clinician-based ratings of depression were consistent with this gender pattern, although not as statistically powerful. While we focused on depression, this differential relationship of gender compared to sex also emerged for hysteria, often correlated with depression and interpreted to reflect the presence of anxiety in the clinical picture (Duckworth & Anderson, 1986). It is possible, therefore, that the role of gender in the clinical expression of schizophrenia is not limited to depression, but to negative affect more generally. Most important to our argument is that gender, not sex, is associated with what have been consistently reported differences in affect of female patients *vis a vis* male patients (e.g. Abel et al, 2010). These gender differences, at least in this study, were impervious to a wide range of sociodemographic and clinical influences. In short, if a person with schizophrenia can be characterized as “feminine”, that person will likely show more affect, especially depression, than will “masculine” individuals independent of sex. It is important to note that the mf scale does not rely on items reflecting negative affect, thereby forestalling the argument that the relationship between gender and depression is a tautology of measurement. We also note that even if gender is embedded in sex (biology; Canli, 2006), the two were statistically independent in this study, supporting different constructs and yielding different outcomes.

What exactly is the MMPI mf scale measuring and why is it such a powerful variable? First, we must concede that we cannot offer what the mf scale exactly measures; this has been a controversial and conflicted area of research for decades (Greene, 1980; Duckworth & Anderson, 1986; Nasser et al 2002). It has been consistently found that in men, both clinical and nonclinical samples, the mf scale is significantly higher among college-educated individuals than those with less education. This was replicated in our study although controlling for education did not affect the ANOVA effect of gender on depression. Thus, while the relationship between MMPI mf and education deserves study, it is not relevant to the primary focus of this study. We suggest that the perspective of personality is the appropriate lens through which to understand our findings and that it may be appropriate to drop the term “gender” altogether and in its place use personality traits. Indeed, there have been reports that the mf scale seems to capture general personality characteristics including affect and social role (Greene, 1980; Duckworth & Anderson, 1986; Nasser, 2002). A major restriction of the mf scale is its bipolarity; that is, masculine and feminine are at opposite ends of the same scale. We know from the work of those such as Bem (1994) that feminine and masculine traits can be independently assessed and lead to a more nuanced understanding of gender. This will be important to incorporate in future research.

Previous attempts to incorporate personality into the study of schizophrenia have focused on the schizotypal personality with the aim of identifying individuals “at risk” for schizophrenia (e.g. Berrantes-Vidal, et al, 2015; Kendler & Walsh, 1995). The study of personality in the “high-risk” context assumes that schizophrenia and personality are non-independent and, further, that personality traits reflect an endophenotype of the full clinical disorder. Personality from this perspective has been used to predict those who will be diagnosed with

schizophrenia from those who will not, rather than asking how personality might account for the heterogeneity within schizophrenia itself.

Those efforts that have directly addressed the problem of heterogeneity in schizophrenia have largely focused on clinical variables such as premorbid development, symptom type, and severity of illness. Onset age, closely linked to patient sex not gender (*qua* personality traits), has been an exception leading to the examination of biological moderators or mediators of the disorder (e.g. Grigoriadis & Seeman, 2002; Kulkarni et al, 2008; Seeman, 1996). The use of sex as an explanatory variable in areas other than onset has not been consistently successful. The results of the current study suggest that this may be due to a conflation of sex and gender differences. More broadly, we view the results as supporting the importance of examining personality differences among those diagnosed as having schizophrenia.

We have for many years ignored individual differences in personality among those with schizophrenia, looking instead at how peculiar personality traits might predict schizophrenia or assuming that schizophrenia all but destroys normal personality, reducing those with schizophrenia to their diagnosis. In contrast, we suggest that personality differences exist in schizophrenia and that they are independent of the disorder. To pursue the idea that personality and schizophrenia are independent however, we will need to be more exact in our use of terms such as sex and gender. It will be important in the future for schizophrenia researchers to report whether they are studying sex or gender more accurately and more importantly to begin to incorporate measures of personality into their studies. To be clear, we are not suggesting personality as potential source of endophenotypes or subclinical expressions of schizophrenia that might be useful in predicting the development of schizophrenia, but rather personality differences as independent of schizophrenia that would be useful in predicting how individuals react to schizophrenia as reflected in its expression and course and in informing treatment.

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Figure 1.
MMPI profile by Sex and Gender: Male Schizophrenia Patients

Figure 2.
MMPI profile by Sex and Gender: Female Schizophrenia Patients

Table 1Means (*s.d.*) of Demographic Characteristics of Patients by Sex and Gender

	WOMEN		MEN	
	Feminine	Masculine	Feminine	Masculine
Age at MMPI	37.9 (11.8)	36.6 (19.7)	34.06 (10.2)	31.6 (8.2)
Race (% white)	80.6	50.0	87.6	72.2
AFH	24.7 (10.3)	26.1 (9.6)	21.9 (6.2)	21.6 (7.2)
Education(Years)	13.2 (2.7)	11.5 (1.5)	13.25 (2.3)	11.9 (1.9)
Duration(Years)	12.9 (8.4)	10.5 (13.7)	12.1 (9.5)	9.9 (6.7)

Note: MMPI = Minnesota Multiphasic Personality Inventory; AFH = age of first hospitalization

Age MMPI: Sex, $F_{1, 209} = 4.253, p = .04$

AFH: Sex, $F_{1, 207} = 5.639, p = .018$

Education: Gender, $F_{1, 206} = 10.464, p = .001$