

Sex, Affect, And Cognitive Perseveration In Schizophrenia

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Citation

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Abstract

Objectives: The current study sought to examine the relationship between sex, affect, and Wisconsin Card Sorting Test perseveration in 125 individuals with schizophrenia and schizoaffective disorder to identify whether negative affect acted as a mediator and whether sex differences existed on BDI-II depression, BAI anxiety, PANAS negative affect, and WCST perseveration. **Design:** This was a cross-sectional study with participants recruited from a local outpatient facility. This design was used to address our study objectives of identifying a mediator and/or sex differences as they currently exist in this sample of adult individuals. **Methods:** Participants signed study consent forms, then completed a sociodemographic form, the Beck Anxiety Inventory, the Beck Depression Inventory-II, and the Positive and Negative Affect Schedule. Participants were also administered the Wisconsin Card Sorting Test. **Results:** Primary findings included a lack of support for the mediator hypothesis but the existence of a significant sex by Beck Anxiety Inventory score interaction, reflecting a significant difference in perseveration between men with minimal/mild anxiety scores and moderate/severe anxiety scores. The difference in mean perseveration scores between women with minimal/mild and moderate/severe anxiety scores was not significant. **Conclusions:** Men were more perseverative in the presence of anxiety. Women, however, were less perseverative at higher levels of negative affect than at lower levels of negative affect, although this difference was nonsignificant. This pattern of sex differences is discussed from several perspectives including the Taylor-Spence drive theory.

INTRODUCTION

The expression of schizophrenia is different in women and men (¹, ²). Generally, women tend to have better premorbid levels of functioning, a later onset, a more affective clinical expression (including higher levels of depression and anxiety), and a better long-term outcome than do men. While these characteristics are arguably not specific to schizophrenia, they do address at least partially the “heterogeneity problem” that has long-plagued schizophrenia. They suggest, at a minimum, two subtypes of the disorder associated with sex (male, female) that in turn hint at different developmental paths to psychosis and its treatment. It has even been suggested that the two sexes represent fundamentally different etiological pathways, with men exhibiting less of a familial and women exhibiting more of a familial form of the disorder (¹; see also ²).

Interestingly, the evidence for sex differences in neuropsychological functioning has been far less consistent. Some studies have pointed to greater neuropsychological impairment in men, some in women, and some no difference (see ¹ for an extensive review of this literature). Our interest in cognitive sex differences and, in particular, cognitive perseveration has been piqued as a consequence of

reviewing two literatures that, when combined, predict that women with schizophrenia should be more perseverative than men with schizophrenia.

The first is the schizophrenia literature that supports greater negative affect in female than male schizophrenia patients. One study found that women with schizophrenia had increased negative affect in response to stress than men with schizophrenia based on self-reports in accord with the Experience Sampling Method (ESM) (³). Also, in a sample of individuals with either schizophrenia or schizophreniform disorder, women had more severe symptoms of depression and anxiety than men as reflected in the depressive/anxiety scores of the Positive and Negative Syndrome Scale (PANSS) (⁴). In addition, depression and anxiety were more common among women than men in individuals with schizophrenia or schizoaffective disorder with comorbid substance abuse (⁵). In short, women with schizophrenia report and are rated to have higher levels of depression and anxiety than men with schizophrenia. The importance of this association between affective expression and sex emerges clearly in reviewing the second literature.

This second literature points to an association between

negative affect, such as anxiety and depression, and rumination or inflexibility, a form of cognitive perseveration. “Perseveration” is commonly used in the context of schizophrenia, while “inflexibility” and “rumination” tend to be used in the study of affective disorders. The terms are sometimes used synonymously, although the details of the conceptual constructs and theoretical implications differ (see ^{6, 7, 8}). All three are often measured with the Wisconsin Card Sorting Test (WCST) which includes perseverative indices (for example, ^{7, 8}). From the perspective of a shared behavioral measure, it has been shown that WCST perseveration is related to negative (anxiety and depression) affect (e.g., ^{9, 8}). Furthermore, negative affect was linked with perseveration with the proposition that a person becomes depressed as a result of an inability to prevent prolonged self-focus due to engagement in self-regulation (¹⁰). In a similar vein, rumination was found to be positively correlated with depression and anxiety in a sample of undergraduate students (¹¹). It appears, in short, that cognitive inflexibility, rumination, and perseveration are linked to negative affect states in both clinical and non-clinical samples.

Why perseveration? Why sex differences? If perseveration is a marker for schizophrenia, or at least related to its negative symptoms, as some suggest (¹²), then it is critical to know if such a presumed marker is equally salient in men and women. Independent of perseveration’s potential status as a schizophrenia marker, there is sufficient evidence to suggest that affect may play a causal role in perseveration so that examination of affect and perseveration in schizophrenia will inform our understanding of this executive dysfunction. There is at least one study (to our knowledge) that supports the integration of affect and cognition in the study of perseveration in schizophrenia. Subjective feelings of depression and dejection were associated with poor performance in executive functioning, a domain which included WCST perseverative responses, in schizophrenia (¹³). The authors did not, however, report any sex differences.

To summarize: executive dysfunction in the form of cognitive perseveration is critical to our understanding of schizophrenia. Negative affect may be causally associated with cognitive perseveration in other psychiatric disorders, notably anxiety and depressive disorders (e.g., ⁹). Given that women with schizophrenia have been reported to exhibit more negative affect than men with schizophrenia, we hypothesized that female schizophrenia patients would

exhibit greater perseveration than men and that this relationship (i.e., sex and perseveration) would be mediated by negative affect.

METHODS

PATIENTS

One hundred and thirty-seven patients were recruited through four community mental health services sites and completed study consent forms. Eight individuals (two males, six females) were unable to complete at least the Wisconsin Card Sorting Test (WCST), which was administered first in the set of cognitive measures following administration of the affective measures, and were therefore excluded from any further analyses. The non-completers were not significantly different from the completers on either sociodemographic or clinical variables. Four individuals (three males, one female) were excluded due to a diagnosis other than schizophrenia or schizoaffective disorder. The final sample included 125 individuals with a DSM-IV diagnosis of either schizophrenia ($n = 75$) or schizoaffective disorder ($n = 50$) and who were able to complete all affective measures and the WCST at minimum. There were missing cognitive data for 10 of these individuals as a result of either patient fatigue or test administrator error.

Of the 125 individuals used in the analyses, 74 were males and 51 were females. The mean age for males was 43.8 with a standard deviation of 8.1 and the mean age for females was 42.7 with a standard deviation of 7.3. Fifteen males and eight females were Caucasian while 58 males and 43 females were African-American. Only one male participant was Asian. Forty-eight males and 27 females were diagnosed with schizophrenia and 26 males and 24 females were diagnosed with schizoaffective disorder. The vast majority of patients ($n = 117$) were unemployed at the time of assessment. This was a chronically ill group of individuals, many with multiple hospitalizations. All were prescribed medication at the time they were participants in this study. Refer to Table 1 below for demographic and clinical characteristics.

Figure 1

Table 1 Demographic and Clinical Sample Characteristics

Sex	74 Males 51 Females
Race	23 Caucasians 101 African Americans 1 Asian American
Age	Mean = 43.3 Standard Deviation = 7.7 Median = 44
Diagnosis	75 (schizophrenia) 50 (schizoaffective disorder)

MEASURES

DSM-IV diagnosis was based on the individual's most recent diagnosis recorded on the patient roster and medical records that reflected formal psychiatric evaluation reviewed at regular periods.

Sociodemographic Form: This standard set of variables included race, age, marital status, education, employment history, medications, treatment history, and family history of psychiatric disorder.

Clinical measures: (1) Beck Depression Inventory-II (BDI-II; ¹⁴), (2) Beck Anxiety Inventory (BAI; ¹⁵), and (3) the Positive and Negative Affect Schedule (PANAS; ¹⁶).

The BDI-II is a reliable and valid 21-item, self-report measure of depressive symptoms, including suicidal thoughts or wishes, loss of interest, and concentration difficulty (¹⁴). The participant is required to choose one response per item on a scale from zero to three where zero indicates no problems in the specific area. A participant's total score falls between zero and 63 and is classified as minimal (0-13), mild (14-19), moderate (20-28), or severe (29-63) (¹⁴). This measure was chosen based on its reliability, validity, and popularity as a measure of depression. The time required for administration of this measure is between five and ten minutes (¹⁴).

The BAI is a reliable and valid 21-item, self-report measure of symptoms associated with anxiety, including numbness or tingling, feeling hot, dizzy or lightheaded (¹⁵). The participant is required to choose one response per item on a scale from zero to three where zero indicates no problems in the specific area. A participant's total score falls between 0 and 63 and is classified as minimal (0-7), mild (8-15), moderate (16-25), or severe (26-63) (¹⁵). This measure was chosen based on its reliability, validity, and popularity as a

measure of anxiety. The time required for administration of this measure is between five and ten minutes (¹⁵).

The Positive and Negative Affect Schedule (PANAS; ¹⁶) is a brief, 20-item scale assessing positive and negative affect on a 5-point scale ("very slightly or not at all" to "extremely"). This measure was chosen due to its specific assessment of negative affect, its reliability and validity, and its brevity. This assessment includes words that reflect generic negative affect such as "irritable", "afraid", and "hostile".

One cognitive measure was used for the purposes of assessing perseveration: the Wisconsin Card Sorting Test (WCST; ¹⁷). The Wisconsin Card Sorting Test (WCST; ¹⁷) is a 128-card computerized assessment used to measure executive function related to frontal lobe function. It is a matching task that requires subjects to sort cards based on color, number, or form. Participants are also informed about whether their sorts are correct or incorrect, but are not informed as to which sorting scheme is used. This measure was chosen not only because of its popularity, but also because of its specific ability to assess for perseveration.

PROCEDURES

Approval for this study was attained by both the University of Louisville IRB as well as by the outpatient treatment facility's IRB. IRB-approved brochures were placed at each outpatient site for the purpose of participant recruitment. Potential participants interested in the study were given a number to call for more information. Once an individual decided to participate in the study, he or she read and signed consent forms. Each participant was paid five dollars upon completion of his or her participation. Participants were given the measures in the following order:

Sociodemographic Form

Beck Depression Inventory-II (BDI-II)

Beck Anxiety Inventory (BAI)

Positive and Negative Affect Schedule (PANAS)

Wisconsin Card Sorting Test (WCST)

The WCST was administered after the affective measures as it is a longer test that is more likely to result in patient fatigue.

DATA ANALYSIS

All analyses were completed with SPSS. First, we tested the mediator status of affect following the correlational

procedures described in the literature⁽¹⁸⁾, which identifies correlations as a precursor to an actual test of mediation (regression), the latter of which is not completed in the absence of significant correlations. In this study, in order to proceed to a regression analysis to identify mediation, the correlations between a) sex and negative affect, b) negative affect and perseveration, and c) sex and perseveration must all reach significance. Here we have three different models, each with a different variable for negative affect: BDI-II depression, BAI anxiety, and PANAS negative affect. The three correlations in each model (a, b, c, above) must reach significance before moving onto regression.

Second, we examined sex differences in two analyses. The first of these was a series of t-tests to test the significance of sex differences on each of the primary variables of interest (BDI-II depression, BAI anxiety, PANAS negative affect, WCST perseveration). The second employed 2 (sex) X 2 (affect) ANOVAs on WCST percent perseverative errors. Separate ANOVAs were conducted for depression, anxiety, and negative affect, each of which was collapsed into the clinical categories of “minimal/mild” versus “moderate/severe” based on published clinical cut scores (see above for published cutoff scores on the affective measures). We used a median split for PANAS negative affect (scores from the minimum of 10 through 22 in group one and scores from 23 through the maximum in this sample of 47 in group two) in the absence of previously acknowledged categories for this measure.

RESULTS

For the correlational model using BAI score, the correlation between sex and anxiety (BAI) was statistically significant ($r = .19$, $p = .038$). Neither the correlation between BAI and WCST perseveration nor the correlation between sex and WCST perseveration reached significance. For the correlational model using PANAS negative affect, the correlation between PANAS negative affect and sex approached, but did not reach, significance ($r = .17$, $p = .064$). Neither the correlation between PANAS negative affect and WCST perseveration nor the correlation between sex and WCST perseveration reached significance. Finally, in the model using BDI-II score, the correlation between BDI-II and WCST perseveration approached, but did not reach, significance ($r = .16$, $p = .077$). The correlations between BDI-II and sex and between sex and WCST perseveration did not reach significance. The absence of any model with three statistically significant pairwise correlations rendered any further test of the mediator

hypothesis following the recommendations of the literature⁽¹⁸⁾ unnecessary.

All further analyses are based on the categorization of patients into affect groups reflecting the clinical significance of anxiety, depression, and negative affect. As the results of the correlational analyses precluded further exploration of mediation, the examination of sex differences was undertaken. First, a series of t-tests were completed to identify any potential differences in sex on depression, anxiety, negative affect, or perseveration. Table 2 summarizes the means, standard deviations, and p values of affect and perseveration scores by sex derived from t-tests.

Figure 2

Table 2 Sex Differences on Measures of BDI-II Depression, BAI Anxiety, PANAS Negative Affect, and WCST Percent Perseverative Errors

	Males M (SD)	Females M (SD)	P Value
BDI-II	19.97 (14.18)	22.67 (13.54)	$p = .290$
BAI	15.76 (12.71)	20.75 (13.52)	$p = .038$
PANAS Negative Affect	21.88 (9.22)	24.96 (8.85)	$p = .064$
WCST Percent Perseverative Errors	33.70 (21.22)	31.75 (18.81)	$p = .597$

Women had a significantly higher mean score than men on BAI anxiety ($t_{123} = -2.101$, $p = .038$) and a higher mean score than men that approached significance on PANAS negative affect ($t_{123} = -1.868$, $p = .064$). The following analyses [2 (sex) X 2 (BDI-II depression) ANOVA, 2 (sex) x 2 (BAI anxiety) ANOVA, and 2 (sex) x 2 (PANAS negative affect) ANOVA] were also conducted to further explore the role of sex in perseveration. Specifically, we were interested in the presence of interactions.

The 2 (sex) X 2 (BAI anxiety) ANOVA on WCST percent perseverative errors was statistically significant [$F(1, 121) = 8.567$, $p = .004$], reflecting a significant difference in perseveration between men with minimal/mild anxiety scores and moderate/severe anxiety scores ($t_{72} = -3.102$, $p = .003$). The difference in mean perseveration scores between women with minimal/mild and moderate/severe anxiety scores was not significant. The 2 (sex) x 2 (PANAS negative affect) interaction approached significance [$F(1, 121) = 3.141$, $p = .079$]. Though not the primary purpose of these analyses as we were interested in interactions, we noted a main effect of BDI-II, which approached significance [$F(1, 121) = 3.564$, $p = .061$]. Results are summarized in Table 3 below.

Figure 3
Table 3 Results of 2 (sex) X 2 (affect) ANOVAs

2 (sex) X 2 (BDI-II)	F (1, 121) = 2.239, p = .137
2 (sex) X 2 (BAI)	F (1, 121) = 8.567, p = .004
2 (sex) X (PANAS Negative Affect)	F (1, 121) = 3.141, p = .079

DISCUSSION

Women emerged as exhibiting more anxiety than did the men. This was especially salient for anxiety. The sexes were comparable in their mean perseveration scores. Furthermore, our study failed to support the role of affect as a mediator between sex and perseveration in schizophrenia. It seems unlikely that a constricted range of negative affect scores account for this failure as many patients had scores that were at “clinical levels.” It is possible, that sample characteristics, most notably duration of illness, may have affected our results. Follow-up studies of more recently or acutely ill individuals could provide insight about the possible role of chronicity.

We did find an unexpected interaction between sex and anxiety on perseveration that was largely influenced by the men. That is, male schizophrenia patients with moderate/severe anxiety had a significantly higher mean perseveration score than male schizophrenia patients with minimal/mild anxiety; the relationship between anxiety level and perseveration in women was in the opposite direction, although not significant. That is, in this sample of schizophrenia patients, anxious men were more cognitively rigid than were less anxious men, whereas anxious women were actually less cognitively rigid than less anxious women. These results, while unusual, are not without precedent in the literature. It was reported, for instance, that anxiety was associated with a worse clinical outcome in a group of 50 male schizophrenia patients, while anxiety was associated with a better clinical outcome in a group of 50 women with schizophrenia (¹⁹). The interaction between sex and anxiety on clinical outcome is completely consistent with our findings in perseveration. In a more recent study, it was found that anxiety positively correlated with clinical severity as measured by positive symptoms in male, but not female, schizophrenia patients (²⁰). It appears that anxiety has a disruptive effect on men and at least a neutral if not enhancing effect on women. It must be noted, however, that the performance of both males and females on WCST perseveration was poor (refer to Table 2 for WCST perseveration means).

Why the differential impact of anxiety on men and women?

Turning to the broad literature on the nature of “male personality” (²¹), we can expect that anxiety is less common and therefore more disruptive in men than women. To the extent that men are on average “instrumental” and women are on average “expressive,” the presence of moderate to severe anxiety can be expected to place men at a cognitive disadvantage. If one considers mate selection as studied extensively in evolutionary psychology (for example, see ²²), this issue of anxiety makes sense considering the separate difficulties in long-term versus short-term mating strategies between men and women. This evolutionary perspective does not, however, provide a handy explanation for why women might actually do better, or certainly not worse, under conditions of anxiety.

Further explanations exist. First, it is important to focus on why anyone, regardless of sex, would perform better with more compared to less anxiety (or negative affect). In the literature, an interaction was noted in which individuals with high anxiety did worse than individuals with low anxiety on a difficult task, but better than those with low anxiety on the easy task (²³). The authors noted the consistency of this finding with the Taylor-Spence drive theory (^{24, 25}). The basis of the original theory is that participants with anxiety would exhibit more drive, and therefore learn at a faster rate, than those without anxiety. However, the theory was later revised to also incorporate the idea that anxious as opposed to non-anxious individuals have worse performance with competing response situations, though difficulty level is also confounded in this latter notion (²⁶). The question for the present study is whether the WCST is conceptualized as easy or difficult. For the women, who exhibited better performance with higher anxiety, conceptualization of the WCST as an easy task would render these results consistent with the Taylor-Spence drive theory. Of course, we did not have a difficult task with which to compare the easy (WCST) task (if indeed the WCST is conceptualized as such) so it is perhaps safer to say the findings among women who showed better performance with higher anxiety partially supports the drive theory. However, perhaps it is the case not only that women conceptualized the WCST as an easy task but also that men construed the task as difficult or challenging. The results attained by men would then be consistent with the theory: males with lower anxiety showed better performance. Unfortunately, participants were not asked whether they regarded the task as easy or difficult and, furthermore, the study referenced above (²³) did not involve task perceptions but rather pre-classified the tasks as easy or difficult. Considering the sex component of the present

findings, it would not be clear in any case why females would be more apt to believe the WCST to be easy and the males to believe it to be difficult. One explanation may be provided by work which identified differences between males and females in visual processing (²⁷). Males performed tasks better in far space and females performed better in near space. The visual stimuli of the WCST can be thought of as a near space task.

It is important to bear in mind that there are other factors that could impact perseverative performance on the WCST. One concerns feedback. Participants are told after each trial whether they are correct or incorrect. It would therefore be helpful to know the differential response of males and females to negative feedback. Although there is no literature on sex differences in feedback specifically for the WCST, one study found that following employee evaluations, females expressed that they intended to change job performance more so than males after receiving feedback, although job status (males higher, females lower) accounted for findings (²⁸). However, the sex difference in feedback responsiveness has been noted in other studies (e.g., ²⁹). Perhaps, then, there was a sex difference in response feedback on the WCST. However, given that females may be more likely to make changes after negative feedback, one might have expected females to exhibit less perseveration than they did.

One final consideration regards state-dependent learning. In order to consider this idea's potential impact on the findings, one must consider the learning component of the WCST rather than perseveration. Based on a series of experiments, it was concluded that people selectively learn information congruent with the mood they experience when learning (³⁰). It may be the case that because females tend to have greater negative affect or anxiety than males, their better performance on WCST perseveration when more highly anxious represents mood-congruent learning. That is that they learned the task better when in a mood consistent with their usual presentation (i.e., anxious). Males had lower mean negative affect scores than females. Therefore, perhaps their learning was best, based on WCST performance, when their anxiety and negative affect were lower.

LIMITATIONS

Anxiety had the strongest impact of the negative affects on perseveration. While we have made the general case for the disruptive impact of negative affect on male cognitive function, our data suggest that it was primarily anxiety and

neither depression nor generic negative affect which had this impact. We should note that the results for both depression and negative affect were similar in direction to those of anxiety if not statistically significant. It is possible that future studies will reveal that depression and other forms of negative affect have equally strong effects on perseveration in men. The sample size may not have been sufficiently large enough for depression and PANAS negative affect. Also, this is a cross-sectional study and we do not actually know if anxiety has a causal role. We must acknowledge that while we have used the term "effect" of anxiety on perseveration, as the study is cross-sectional we must wait for a longitudinal, within subject study to provide information about genuine causal effects.

Is the finding specific to schizophrenia? There is no a priori reason to suppose that the results of our study are specific to schizophrenia. Rather, they may reflect generalized sex differences that could be revealed in a comparable analysis of non-clinical samples. As for schizophrenia, this study suggests not only that men and women present with the disorder somewhat differently, but also that emotional context may play an important role in cognition, sometimes in surprising ways.

There are additional limitations. For the purposes of ascertaining internal consistency, computation of Chronbach alpha in this sample would have been beneficial. Also, the goal of the study was to identify participants with a diagnosis of schizophrenia or schizoaffective disorder, but better attention should have been given to comorbid diagnoses as many people had, or likely had, other diagnoses, either other Axis I diagnoses (particularly substance use disorders) or Axis II diagnoses (e.g., personality disorders).

FUTURE DIRECTIONS

This study highlights several possible avenues of future research. First, it would be helpful for this study to be replicated. This is the first time a study such as this was attempted and perhaps a new sample would yield different findings. Second, a greater number of studies comparing different diagnostic groups with schizophrenia on WCST perseveration would be helpful. Third, given the WCST perseveration impairment at all levels of affect in schizophrenia, it would be helpful to see if the same pattern of results for males and females—albeit at lower levels of WCST impairment—would be replicated with a sample of individuals without any form of mental illness. Finally, as

the Taylor-Spence drive theory was discussed in this paper as a possible explanation for our results, future research would be helpful for better evaluating whether this theory applies to other forms of negative affect aside from anxiety.

CONCLUSIONS

This study suggests that negative affect does not mediate sex and perseveration. However, given that this is the first study of its kind, it seems imprudent to immediately dismiss a plausible theory on the basis of non-significant findings. Since this study showed evidence of the possibility that anxiety may contribute to the relationship between sex and perseveration based on the significant ANOVA and the significant correlation between sex and anxiety, it seems that anxiety may prove to be particularly important in the study of schizophrenia. Furthermore, we must consider the possibility that perseveration represents an affective, as opposed to merely a cognitive feature of the illness. Moreover, this study shows that men and women with schizophrenia do not present in the same way, at least not affectively. This has important implications for the treatment of individuals with schizophrenia who may be better served by strategies which take their sex (male vs. female) and anxiety affect into account.

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