Does sex influence the relation between symptoms and neurocognitive functions in schizophrenia?

Ashok K. Malla, MB; Ross M.G. Norman, PhD; Sandra Morrison-Stewart, PhD; Peter C. Williamson, MD; Edward Helmes, PhD; Leonard Cortese, MD

Malla, Norman, Williamson, Cortese — Department of Psychiatry, University of Western Ontario and London Health Sciences Centre, Victoria and University Campuses, London, Ont.; Morrison-Stewart — North Bay Psychiatric Hospital, North Bay, Ont.; Helmes — Department of Psychology, Edith Cowan University, Perth, Western Australia

Objective: A secondary analysis of our data to investigate if sex influences the specificity of the relationship between each of the 3 clinical syndromes (i.e., reality distortion, disorganization and psychomotor poverty) in schizophrenia and the neurocognitive functions that are thought to represent regional brain functions. Patients and Design: Fifty-seven male and 30 female patients with a DSM-III-R diagnosis of schizophrenia were rated on the Scale for Assessment of Negative Symptoms and the Scale for Assessment of Positive Symptoms to derive scores for psychomotor poverty, disorganization, and reality distortion syndromes. All subjects completed a battery of neuropsychological tests purported to assess functioning of left temporal, right temporal, left basal frontal, right basal frontal, and dorsolateral prefrontal cortex. Results: Correlation coefficients between syndrome scores and neuropsychological measures showed only word fluency (left frontal functioning) to have a statistically significant association with psychomotor poverty in women (p < 0.01). This relation was specific to psychomotor poverty syndrome. No relations between neurocognitive measures and symptoms were seen in men. Conclusions: The lack of specific relations between symptom dimensions in schizophrenia may be influenced by the fact that the neuronal circuitry associated with particular symptom dimensions may differ in men and women.
Symptom heterogeneity\(^1\) and significant sex differences\(^2\) may account for some of the equivocal results of investigations of brain dysfunction in patients with schizophrenia. In an attempt to understand this symptom heterogeneity, Liddle\(^3\) proposed a 3-syndrome model of symptoms consisting of psychomotor poverty (core negative symptoms), disorganization (thought disorder and bizarre behaviour), and reality distortion (delusions and hallucinations); this model has received some empirical support.\(^4\)–\(^6\) Each of the dimensions of psychopathology in schizophrenia is hypothesized to be related to functional deficits in specific areas of the brain;\(^7\) psychomotor poverty is thought to be associated with dysfunction of the dorsolateral prefrontal cortex, disorganization with dysfunction of basal orbitofrontal cortex, and reality distortion with anomalies in temporal lobe functioning.

Although several earlier studies\(^8\)–\(^10\) provided evidence that these clinical syndromes were associated with different patterns of neuropsychological dysfunction, when we tested 87 patients diagnosed with schizophrenia, we failed to find evidence to support Liddle’s hypothesis of a specific relation between psychomotor poverty and dorsolateral prefrontal cortical functioning or between disorganization and mediobasal prefrontal cortical functioning.\(^11\) We did, however, find evidence that reality distortion was related to impairment of verbal memory, which likely reflects left temporal lobe functioning.

There are several possible reasons for this lack of consistency in the relation between symptom dimensions and neurocognitive functions. For example, neurocognitive measures may not be specifically related to functioning of any particular cortical region but may more likely reflect functioning of a circuitry involving cortical and subcortical structures. Also, given the differences reported between men and women in relation to many aspects of schizophrenia,\(^7\) variations in the proportions of men and women in patient samples in different studies may be another source of this inconsistency. If there are significant sex differences in the nature or expression of schizophrenia, such differences are likely to influence our interpretation of relations between brain functional measures and symptom dimensions.

Results from studies on sex differences and cognitive deficits have been equivocal. Although some have reported more deficits in men,\(^12\) others have found the opposite,\(^13\) and still others have reported no sex differences in neuropsychological performance deficits in patients with schizophrenia.\(^14\) There is, however, evidence of sex differences in the functional organization of the central nervous systems of men and women.\(^15\) This suggests that even if there are no sex differences in the absolute level of cognitive deficits, there may be significant sex differences in the relations between clinical symptoms and variables assessing brain function. For example, sex differences in the relation between symptom dimensions and EEG coherence between left frontal and temporal regions,\(^16\) and between symptom dimensions and neurological “soft signs”\(^17\) have been reported. Therefore, it is possible that even if there are no “absolute” symptom or neurocognitive differences between men and women, neurocognitive correlates of symptoms may vary as a function of sex.

We examine the hypothesis that the nature of the relation between neurocognitive measures and psychomotor poverty, reality distortion, and disorganization, respective, is likely to be different in male and female patients with schizophrenia, irrespective of differences in the level of symptoms or neuropsychological performance.

**Method**

A total of 57 male and 30 female subjects with a diagnosis of schizophrenia, confirmed though a Structured Clinical Interview for DSM-III-R (SCID), gave informed consent agreeing to complete the study. Demographic and clinical data, including age, education, age of onset, and length of illness, were recorded for all subjects.
Symptoms, assessed using the Scale for Assessment of Negative Symptoms (SANS)\textsuperscript{18} and the Scale for Assessment of Positive Symptoms (SAPS),\textsuperscript{19} were rated in relation to each patient’s experience and behaviour in the previous month. Symptoms were rated by senior clinicians (A.M., R.M.N., and L.C.) who had established inter-rater reliabilities on these rating scales in a previous study.\textsuperscript{20} The scoring of the 3 syndromes was based on the method used by Liddle.\textsuperscript{7,9,11} Psychomotor poverty was scored by adding scores on items of poverty of speech, decreased spontaneous movement, and the average of 4 items reflecting blunting of affect (i.e., affective non-responsivity, unchanged facial expression, paucity of expressive gestures, lack of vocal inflections); disorganization syndrome score was the sum of scores for items measuring inappropriate affect, poverty of content of speech, and the global rating of positive formal thought disorder; reality distortion syndrome was the sum of items concerning auditory hallucinations, commenting on the patients’ behaviour, persecutory delusions and delusions of reference.

**Neuropsychological measures**

Neuropsychological measures were chosen according to their ability to reflect brain function in areas hypothesized to be related to each of the 3 syndromes. The following neuropsychological tests were administered: the Wisconsin Card Sorting Test\textsuperscript{21,22} (percentage of perseverative errors) for left dorsolateral cortical functioning, the Design Fluency Test (DFT)\textsuperscript{23} and the Chicago Word Fluency Test (CWFT)\textsuperscript{24} for right and left basal frontal functioning, respectively, the Rey Auditory Verbal Learning Test (RVLT)\textsuperscript{25} and the Logical Memory Test of the Wechsler Memory Scale — Revised (WMS-LM)\textsuperscript{26} for left temporal lobe functioning, and the Benton Visual Retention Test (BVRT) and Rey-Osterrieth Complex Figures Test (ROCFT)\textsuperscript{27} for right temporal lobe functioning.

For a more detailed description of the methodology, see Norman et al.\textsuperscript{11}

**Data analysis**

Means and standard deviations for demographic, clinical, and neuropsychological variables were compared between men and women using \(t\)-tests for continuous and \(\chi^2\) for categorical variables. Pearson correlation coefficients were calculated between each of the 3 syndromes and neuropsychological measures, for men and women separately. Any significant correlations were contrasted between male and female subjects within each syndrome using standard 2-tailed \(t\)-tests for contrasting correlations between independent samples.

**Results**

Table 1 summarizes the relevant demographic and clinical characteristics of the 57 male and 30 female patients who completed the neuropsychological protocol and the symptom assessment. Only the mean age (30.5 [standard deviation (SD) 7.1] years for men v. 37.4 [SD 9.0] years for women, \(p < 0.001\)) and mean disorganization score (3.9 [SD 3.9] v. 1.9 [SD 2.3], \(p < 0.005\)) were significantly different between male and female patients. Significant differences were also found between the standard deviations.

For the SANS, the intraclass correlation coefficient

<table>
<thead>
<tr>
<th>Table 1: Demographics and clinical characteristics of men and women diagnosed with schizophrenia who completed the neuropsychological assessments</th>
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<td>Characteristic</td>
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<tr>
<td>Mean age (and SD), yr*</td>
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<tr>
<td>Mean length of illness (and SD), yr</td>
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<tr>
<td>% with at least a high school education</td>
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<td>N. of hospital admissions (and SD)</td>
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<td>Daily chlorpromazine equivalence, mg</td>
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<td>Mean psychomotor poverty score (and SD)</td>
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<td>Mean disorganization score (and SD)</td>
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<td>Mean reality distortion score (and SD)</td>
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SD = standard deviation.

*\(p < 0.001\).

†\(p < 0.005\).
(ICC) for the summary score (total of global ratings) was 0.60 and for the composite score (total specific symptom rating) was 0.68. For the SAPS, the ICC for the total summary score was 0.84 and for the composite score 0.83.

The average ICC for items comprising each of 3 syndromes were as follows: psychomotor poverty 0.49, disorganization 0.60, and reality distortion 0.66. There were no significant correlations between the 3 syndromes for either male or female subjects, implying dimensional independence of the 3 syndromes.

As can be seen in Table 2, there were no significant sex differences on any of the neuropsychological indices either.

Correlation coefficients were calculated to assess the relation between each of the 3 syndromes and the neuropsychological measures for male and female subjects separately (Table 3). Because of the large number of correlations generated, only the correlations with a \( p \) value < 0.01 (2-tailed) were regarded as significant.

For women, but not men, the negative correlations between psychomotor poverty and scores on word fluency, design fluency and logical memory were significant (lower scores on each of these tests indicate greater impairment). In an attempt to determine if the relation between impairment on the 3 neuropsychological measures and psychomotor poverty was specific to that particular syndrome, the correlations for women between verbal memory (WMS-LM), word fluency (CWFT), and design fluency (DFT), and psychomotor poverty were contrasted with those between each of these 3 measures and disorganization and reality distortion syndromes. These weighted contrasts showed that only the relation between word fluency and psychomotor poverty was significantly greater than the relation of word fluency to reality distortion and disorganization syndromes (\( t = -2.17, p < 0.04 \), 2-tailed). A contrast of this relation between men and women revealed a significant difference (\( t = 2.03, p < 0.05 \), 2-tailed), but no other significant associations between syndromes and neuropsychological indices were observed.

Partial correlations, calculated to remove the variance attributable to age, medication (chlorpromazine equivalent), and length of illness in all of the above correlations, did not change the strength of the associations significantly.

**Discussion**

Examining the relation between neuropsychological test performance and syndromes separately for men and women had 2 implications for the power of our statistical tests. First, our sample sizes were reduced, and second, we chose a more conservative level of...
significance (i.e., p value < 0.01) than is often used. However, our results strongly suggest that sex may modify relationships between symptom dimensions and neurocognitive functions in schizophrenia and that negative symptom dimension (i.e., psychomotor poverty) may be related to bifrontal and left temporal brain functions in women, but not in men. The failure to find neuropsychological tests specifically associated with only 1 syndrome is consistent with the tendency of each to be predominantly, but not solely related to specific areas of brain function.11

Why we should detect a sex difference in the pattern of associations between clinical syndromes and neuropsychological measures is unclear. The finding is unlikely to reflect sex differences in variances associated with each of the symptom dimensions or neuropsychological indices; only disorganization syndrome showed a significant difference between men and women in means and SDs, but there were no sex differences found in the relation of neuropsychological measures with any of the syndromes. Mean age, the only other difference found between male and female subjects, was unlikely to have influenced our results; partialling out the effect of age on any of the significant correlations did not alter the strength of the relations. It is also unlikely that the association between word fluency and psychomotor poverty is related to higher doses of chlorpromazine taken by women; our data failed to show any sex difference in mean dose of chlorpromazine equivalent. In addition, partialling out the effect of medication had no impact on the strength of the association. Although we have no reason to suspect any differences in syndrome ratings received by male and female patients, such a possibility exists; however, our relatively small sample sizes did not allow such an examination of the data.

It is possible that the same neuronal circuitry serves different functions in men and women, implying differences in the organization of brain functioning.15 Thus, the same symptoms may require impairment of different neuronal circuitry in male and female patients with schizophrenia. It is also possible, however, that each neuropsychological measure may be related to functions of different areas of the brain in men and women, although there is no evidence of this in tests of healthy men and women.

Despite similarities in the symptom ratings and impairment scores on neuropsychological tests, different pathophysiological processes may operate in men and women with schizophrenia to produce negative symptoms. It is possible that symptoms and cognition may be more independent dimensions in men than they are in women with schizophrenia. Our findings are, at best tentative, and must be replicated in an independent sample with larger samples.

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References


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Applications should arrive by January 31, 2001. Travel bursaries will be awarded to those who submit the best abstracts.

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