Cognitive Asymmetry Patterns in Schizophrenia: Active and Withdrawn Syndromes and Sex Differences as Moderators

by John H. Gruzelier, Lesley Wilson, David Liddiard, Emanuelle Peters, and Lillian Pusavat

Abstract

Recognition memory for words and faces was examined in male and female schizophrenia patients for evidence of associations between putative left–right hemisphere asymmetry patterns and active (positive) versus withdrawn (negative) syndromes. Ninety-five normal controls and 104 schizophrenia patients with active, withdrawn, and mixed syndromes or in symptom remission were examined, including an unmedicated subgroup. Memory was poorer in patients than controls, while the remitted group had superior memory to psychotic patients. Active and withdrawn patients showed the hypothesized syndrome-dependent cognitive asymmetries: active (word > faces); withdrawn (faces > words), except active females who showed a word deficit. The results support selective lateralized temporoparietal impairment of either hemisphere in schizophrenia, with laterality related to active (face memory/right-sided impairment) and withdrawn (word memory/left-sided impairment) syndromes, except active syndrome females. These syndrome-related asymmetries moderated the sexually dimorphic asymmetries found in normal subjects. Consideration of individual differences both in sex and syndromes based on activity and withdrawal, and of left and right hemisphere memory modality, may assist in unraveling heterogeneity in schizophrenic cognition. The superior memory of recovered patients indicates that some memory impairment in schizophrenia is functional.

Key words: Recognition memory, word memory, face memory, syndromes, activity, withdrawal, sex differences.


In schizophrenia, learning and memory functions have been found disproportionately impaired relative to other cortical functions in both inpatients and outpatients and therefore may be of singular importance to the nature of schizophrenic pathology (McKenna et al. 1990; Saykin et al. 1991). The apparent selectivity of these processes is important, given that one of the more reliable findings from neuropathological and functional imaging studies of schizophrenia has been evidence of temporal lobe abnormalities, with particular involvement of the hippocampal system (Falkai and Bogerts 1986; Altschuler et al. 1987; Benes 1989; Jeste and Lohr 1989; Tamminga et al. 1992). Lateralized structural deficits, particularly of the left temporal lobe, have also been reported in schizophrenia and schizophréniform illnesses (Colter et al. 1987; Gur et al. 1991; DeLisi et al. 1989; Bogerts et al. 1990). This evidence favors a possible structural substrate to memory impairments in schizophrenia.

An earlier report comparing schizophrenia patients, affective psychotic patients, and controls (Gruzelier et al. 1987, 1988) confirmed evidence of lateralized deficits on tests of learning and memory in schizophrenia. The tests included Hebb's recurring digit span test, Corsi's recurring block span test, and tests of verbal and nonverbal conditional associate memory that had been developed to assess unilateral temporo- and fronto-hippocampal functions (Milner 1982). Aside from evidence of generalized impairment, schizophrenia patients were particularly deficient on the test of left temporo-hippocampal function. However, when individual differences were considered, some patients' right hippocampal functions were more impaired than their left-sided functions. Reviews have shown that hemispheric asymmetry patterns involving the right hemisphere in schizophrenia patients are by no means incidental, but they have received less attention than the more commonly reported left-sided deficits (Gruzelier 1983, 1991; Cutting 1990).

Of potential importance to the commonly reported undefined heterogeneity in schizophrenia is our previous...
finding that the two opposite patterns of lateral asymmetry were syndrome related: Left-sided impairments were associated with a withdrawn (negative) syndrome, and right-sided impairments with an active (positive) syndrome (Gruzelier et al. 1987, 1988). We had originally found that active versus withdrawn descriptors best characterized two syndromes that had been delineated by classifying schizophrenia patients on the basis of lateral asymmetries in electrodermal orienting responses (Gruzelier and Manchanda 1982). Electrodermal responses had been targeted because of hypothesized lateralized limbic involvement in modulation of electrodermal orienting and habituation (Gruzelier 1973); recent intracranial stimulation studies in man have shown that asymmetries in electrodermal activity were particularly marked with unilateral stimulation of the amygdala, hippocampus, and cingulate (Mangina and Beuzeron-Mangina 1996).

Activity–withdrawal had been earlier suggested to be central to positive–negative syndrome distinctions in schizophrenia (Wing and Brown 1970; Depue 1976), but “activity” and elevated mood were lost sight of in 1980s’ formulations of positive and negative symptoms. Key features of our active syndrome were raised levels of activity, pressure of speech, accelerated cognition, positive or labile affect, and affective delusions. The withdrawn syndrome consisted of poverty of speech, blunted affect, social and emotional withdrawal, and motor retardation. The distinction was not a simple positive–negative symptom dichotomy because both syndromes coexisted with Schneiderian symptoms. Approach (left hemisphere) and withdrawal (right hemisphere) have been considered by some as fundamental to hemispheric specialization and to neurochemical asymmetries (Kinsbourne 1982; Tucker and Williamson 1984; Davidson and Tomarken 1989). We have theorized that this dichotomy has many affinities with the nature of the symptoms and behavioral signs inherent in the active–withdrawn distinction in schizophrenia as well as in schizotypy (Gruzelier 1991, 1996b).

Whether recognition memory, as distinct from total recall, is deficient in schizophrenia has been controversial (Koh 1978; Neale and Oltmanns 1980; Calev and Monk 1982). There has also been uncertainty as to whether visual memory is affected to the same extent as verbal memory (Calev et al. 1991). Evidence of syndrome-related individual differences in patterned deficits may go some way toward resolving these inconsistencies. Here, a syndrome analysis of patterns of cognitive asymmetry is conducted on a large sample of schizophrenia patients (N = 104) who are compared with normal controls using a test of recognition memory for words and unfamiliar faces. If schizophrenia does involve the temporal lobe, then recognition memory should be affected because the temporal lobe is thought to play a major role in recognition memory (Squire and Zola-Morgan 1991; Treves and Rolls 1994). The chosen words and faces test would be suitable to answer the laterality question because it fulfilled the criterion of double dissociation by successfully distinguishing left from right temporal and parietal lobe impairment in neurological patients; the word test was also sensitive to left frontal deficits (Warrington 1984).

Sex is an individual difference that is fundamental to hemisphere asymmetry. A body of evidence suggests that women are less lateralized than men, at least for verbal abilities (e.g., Shaywitz et al. 1995). Alternatively, the within-hemisphere organization of functions, especially verbal abilities, differs between the sexes (Kimura 1992). The word and face recognition memory tests are particularly germane to this issue as they have disclosed a sex difference in five adult samples: females showed a word advantage, while males showed a face advantage (Gruzelier 1994). Furthermore, in both sexes reversed asymmetries in one study were associated with masculinity in women and femininity in men. Sex differences in the form, course, and expression of schizophrenia are well accepted (Lewine 1981) but are seldom considered in the context of the neuropsychology or neuropathology of schizophrenia (Goldberg et al. 1995). Stratification of syndrome by sex was a feature of the present investigation.

Here, we offer a theory-driven investigation of differential deficit in syndromes of schizophrenia based on what was originally a data-driven syndrome-asymmetry model (for a review, see Gruzelier 1996a, 1999a). Predictions were as follows: Patients with an active syndrome would have superior recognition memory for words than faces, reflecting the hypothesized left > right hemispheric activation pattern associated with this syndrome; by contrast, withdrawn syndrome patients would have superior memory for faces than for words, consistent with right > left hemispheric activation. In view of the reported bilateral involvement of verbal abilities in females, in the left-hemisphere-reliant active syndrome the predicted relations may be stronger in male than in female patients. Although we included a healthy control group, we are conservative about the significance of differences between patients and healthy controls in view of general performance deficit in patients (Chapman and Chapman 1973).

Methods

Patients. One hundred and sixteen schizophrenia patients and 95 normal controls were tested. Patients fulfilled DSM-III-R criteria (American Psychiatric
Cognitive Asymmetry Patterns


Association 1987). Controls were hospital staff. All subjects were strongly right handed (scores > 69) as measured with the Edinburgh scale (Oldfield 1971). Exclusionary criteria in the recruitment of patients were electroconvulsive therapy in the current episode or in the previous 6 months, evidence of neurological damage, nonpsychiatric medical disorders, age greater than 55 years, IQ below 80, or fewer than 10 years of education, and, in the case of controls, medical or psychiatric illness and medication of any kind. Subjects were excluded from the analyses if scores on the memory tests were both less than 30, suggesting chance performance, coupled with evidence of stereotyped responding such as a run of eight or more “yes” or “no” responses. Twelve patients were excluded on this basis, reducing the patient sample to 104. In the patient group 66 were male and 38 female with an average age of 34.24 years (standard deviation (SD) = 8.22); in the control group 45 were male and 50 were female with an average age of 33.32 years (SD = 8.93). The controls and patients did not differ in age (F = 1.88). Stage of the menstrual cycle was not controlled for.

As in the previous report (Gruzelier et al. 1988), patients were classified into active and withdrawn syndromes. They were designated as remitted if they were awaiting discharge or were outpatients (about half this group) and if they fulfilled rating criteria for symptom remission. Group allocation was on the basis of ratings with a scale consisting of the following six bipolar items of observed behavior ranging from -2 to +2: slowness of movement–overactivity; anergic thinking–flight of ideas; reduced speech–pressure of speech; depressed mood–elated or labile mood; social withdrawal–overinvolvement/attention seeking; blunted affect–emotional engagement. In addition, 11 reported items consisting of non-Schneiderian delusions were obtained from the Present State Examination (PSE; Wing et al. 1974). Three scores were thus obtained: delusions, positive ratings, and negative ratings. Patients were categorized as remitted if there were no hallucinations or delusions, and if behavioral ratings on the bipolar scales were no higher than ±1 on a single item. Ratings were obtained blind to psychological testing. (The scales and classification details and procedures may be obtained from the authors.)

Mean scores for the syndromes for each sex, together with the number in each group, are shown in table 1. Where patients had features of both active and withdrawn syndromes, they were classified as mixed. As can be seen in table 1, the active syndrome was characterized by delusions and positive symptoms, the withdrawn group by negative symptoms, and the mixed group predominantly by delusions combined with negative symptoms. There were no sex differences in the three categories of symptoms in syndrome comparisons with analyses of variance. However, in females, those with a withdrawn syndrome had more negative symptoms than those with a mixed syndrome (F(2,23) = 15.29, p < 0.0001; Tukey, p < 0.05), a distinction that did not hold for males.

Demographic and other clinical features of male and female syndrome groups are shown in table 2. Analysis of variance showed no syndrome differences or interactions with sex: age (syndrome F = 1.06; syndrome × sex F = 0.62), age at onset of schizophrenia (syndrome F = 0.14; syndrome × sex F = 1.57), total length of time in hospital (syndrome F = 1.84; syndrome × sex F = 1.16), and average premorbid IQ estimated by the National Adult Reading Test (NART; Nelson 1982) (F = 0.18; syndrome × sex F = 0.82). Twenty-one patients distributed across the syndromes either were admitted to the hospital and tested free of antipsychotics or were unmedicated outpatients. Neuroleptic dose expressed as the chlorpromazine

Table 1. Means (standard deviations) of ratings of non-Schneiderian delusions and positive and negative symptoms

<table>
<thead>
<tr>
<th>Variable</th>
<th>Active</th>
<th>Withdrawn</th>
<th>Mixed</th>
<th>Remitted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delusions</td>
<td>Male</td>
<td>3.12 (1.80)</td>
<td>2.65 (1.09)</td>
<td>3.08 (2.29)</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>3.14 (1.07)</td>
<td>0</td>
<td>0.06 (0.24)</td>
</tr>
<tr>
<td>Positive</td>
<td>Male</td>
<td>1.47 (2.76)</td>
<td>0.38 (0.89)</td>
<td>0.92 (1.60)</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>1.29 (1.50)</td>
<td>0</td>
<td>0.44 (0.92)</td>
</tr>
<tr>
<td>Negative</td>
<td>Male</td>
<td>0.18 (0.39)</td>
<td>4.23 (1.44)</td>
<td>3.70 (2.25)</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>0</td>
<td>5.10 (2.14)</td>
<td>2.79 (1.69)</td>
</tr>
</tbody>
</table>
Table 2. Demographic and clinical features of the syndrome groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Active</th>
<th>Withdrawn</th>
<th>Mixed</th>
<th>Remitted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>32.5 (10.4)</td>
<td>32.0 (8.2)</td>
<td>36.6 (7.1)</td>
<td>31.7 (6.6)</td>
</tr>
<tr>
<td>Female</td>
<td>35.3 (6.5)</td>
<td>31.5 (12.5)</td>
<td>35.5 (8.2)</td>
<td>37.5 (7.9)</td>
</tr>
<tr>
<td>Age at onset</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>26.2 (8.0)</td>
<td>24.7 (6.8)</td>
<td>25.9 (5.6)</td>
<td>23.3 (4.1)</td>
</tr>
<tr>
<td>Female</td>
<td>25.7 (4.5)</td>
<td>24.3 (11.0)</td>
<td>24.2 (6.2)</td>
<td>28.4 (6.7)</td>
</tr>
<tr>
<td>Total time in hospital, weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>64.9 (117.0)</td>
<td>45.7 (21.2)</td>
<td>40.6 (34.4)</td>
<td>28.9 (23.0)</td>
</tr>
<tr>
<td>Female</td>
<td>33.5 (29.6)</td>
<td>44.7 (18.4)</td>
<td>46.5 (40.5)</td>
<td>28.9 (22.2)</td>
</tr>
<tr>
<td>NART IQ</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>106.2 (10.4)</td>
<td>108.7 (9.3)</td>
<td>106.4 (11.0)</td>
<td>105.1 (9.5)</td>
</tr>
<tr>
<td>Female</td>
<td>104.8 (16.4)</td>
<td>104.4 (17.8)</td>
<td>112.3 (8.7)</td>
<td>108.9 (14.9)</td>
</tr>
<tr>
<td>Chlorpromazine equivalent</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>843.9 (1092.6)</td>
<td>555.6 (421.6)</td>
<td>784.1 (1133.3)</td>
<td>424.0 (590.5)</td>
</tr>
<tr>
<td>Female</td>
<td>1681.7 (1219.4)</td>
<td>1120.0 (1317.6)</td>
<td>783.9 (579.9)</td>
<td>507.2 (601.8)</td>
</tr>
<tr>
<td>Anti-parkinsonian medication, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>4 (23.5)</td>
<td>7 (63.6)</td>
<td>6 (30.0)</td>
<td>7 (38.9)</td>
</tr>
<tr>
<td>Female</td>
<td>2 (28.6)</td>
<td>2 (40.0)</td>
<td>2 (16.7)</td>
<td>1 (6.7)</td>
</tr>
<tr>
<td>Benzodiazepines, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1 (5.9)</td>
<td>2 (18.2)</td>
<td>3 (15.0)</td>
<td>2 (11.1)</td>
</tr>
<tr>
<td>Female</td>
<td>1 (14.3)</td>
<td>1 (20.0)</td>
<td>0 (0)</td>
<td>2 (13.3)</td>
</tr>
<tr>
<td>Clozapine, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1 (5.9)</td>
<td>0 (0)</td>
<td>4 (20.0)</td>
<td>1 (5.6)</td>
</tr>
<tr>
<td>Female</td>
<td>0 (0)</td>
<td>2 (40.0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>No antipsychotic, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>6 (37.5)</td>
<td>2 (18.2)</td>
<td>5 (25.0)</td>
<td>5 (27.8)</td>
</tr>
<tr>
<td>Female</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>3 (20.0)</td>
</tr>
<tr>
<td>Word memory¹</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>45.24 (5.6)</td>
<td>41.91 (5.2)</td>
<td>39.80 (8.0)</td>
<td>43.89 (5.4)</td>
</tr>
<tr>
<td>Female</td>
<td>36.00 (6.3)</td>
<td>36.00 (11.00)</td>
<td>41.48 (6.5)</td>
<td>46.00 (4.4)</td>
</tr>
<tr>
<td>Face memory¹</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>36.47 (5.4)</td>
<td>39.55 (7.1)</td>
<td>38.30 (6.3)</td>
<td>38.16 (6.6)</td>
</tr>
<tr>
<td>Female</td>
<td>35.29 (7.9)</td>
<td>39.00 (8.5)</td>
<td>34.20 (9.1)</td>
<td>39.00 (6.5)</td>
</tr>
<tr>
<td>Word memory¹ (no drug), Male + Female</td>
<td>47.00 (3.8)</td>
<td>44.33 (4.0)</td>
<td>38.20 (9.1)</td>
<td>45.75 (4.7)</td>
</tr>
<tr>
<td>Face memory¹ (no drug), Male + Female</td>
<td>36.67 (6.0)</td>
<td>38.67 (9.0)</td>
<td>36.60 (5.8)</td>
<td>39.00 (5.2)</td>
</tr>
</tbody>
</table>

Note.—Data are mean (standard deviation). NART = National Adult Reading Test.

¹Data are memory scores.

equivalent did not differ between syndromes ($F = 1.29$), sex ($F = 2.72$) (syndrome × sex $F = 0.92$). Of 96 patients, 31 were receiving the anti-parkinsonian drug procyclidine, 12 patients were receiving benzodiazepines as night medication, and 8 patients were receiving clozapine.

**Test Procedure.** Patients were examined in the laboratory with the NART and the Recognition Memory Test (RMT; Warrington 1984). Some patients had topographical electroencephalograms (EEGs) recorded simultaneously according to procedures described elsewhere (Gruzelier et al. 1990). The RMT examines recognition memory for words and for unfamiliar faces. In each acquisition condition 50 items are presented one at a time for 3 seconds, and the subjects are instructed to indicate whether they liked or disliked the item (i.e., whether they
considered the word or face to be pleasant or unpleasant. They were asked to give an immediate reaction and told that a considered judgment was not necessary. In each recognition condition 50 pairs of items are presented in a forced-choice procedure, one item of which was in the previous list. Here, the order of word and face conditions was randomized. The items were presented for 3 seconds and the response was given orally or, where EEG was recorded, by pressing a button. If subjects could not attend to the task, testing was discontinued.

We have observed that the difficulty of the tests was not comparable in our studies. Raw scores for patients are shown in table 2; for controls they were as follows: words 47.33 (3.11), faces 40.89 (5.30); for males, words 47.17 (3.51) and faces 42.47 (5.36); for females, words 47.48 (2.73) and faces 39.48 (4.89). In each of five samples of normal subjects (n > 600), we found, for both men and women, an average 5-score advantage in favor of the word test (Gruzelier et al. 1990, 1995; Gruzelier and Richardson 1994). The word advantage is evident to some extent in the RMT manual norms, where, for example, a 2-point word/face discrepancy was twice as common as a face/word discrepancy. The word advantage was also found here: Inspection of the raw scores for controls indicated a discrepancy between word and face scores of 6.44, and for patients a discrepancy of 5.65, both in favor of word scores. This was confirmed in a repeated measures multivariate analysis of variance (MANOVA) with group (patients/controls) and sex and memory modality (words/faces) as factors, where the memory modality effect was highly significant (F = 133.80, df = 1,195, p < 0.0001), an effect not influenced by group or by sex. Accordingly, in preference to using scaled scores, it was decided to adopt the standard neuropsychological procedure of z-transformation of the word and face scores, each with a mean of zero and a standard deviation of 1.00, as we have done in applications of the same memory test in normal subjects (Gruzelier and Richardson 1994; Gruzelier et al. 1995; Gruzelier 1996a, 1996b; Gruzelier and Doig 1996). The controls were used as a reference group. While it will be seen that the patients had poorer performance than the controls, distributions of discrepancy scores between words and faces (the main interest of the investigation) did not differ (r = 0.45). All asymmetry differences between patient subgroups that achieved levels of statistical significance retained significance when the z-transformation was performed on the patient data alone. Above the age of 39 years, an improvement in memory for faces and a decline in memory for words has been reported (Warrington 1984); however, subdivision of subjects by age (< 40 = 72; > 39 = 30) disclosed neither differences in word memory (F = 1.37) or in faces memory (F = 0.19), nor an interaction between age and memory modality (F = 1.51).

### Results

Means and standard deviations of standardized memory scores for each sex separately for the various syndromes and remitted and control groups are shown in table 3. Groups were compared with repeated measures MANOVA (Statistical Package for Social Sciences) with group and sex as between factors and memory modality as a within-subject factor. Results are shown in figure 1 for male and female groups and in figure 2 for the unmedicated subgroup.

**Controls.** In a MANOVA with sex and memory modality as factors, a main effect of sex showed a memory advantage to males just short of significance (F(1,93) = 3.79, p < 0.055). There was an interaction between sex and memory modality (F(1,93) = 8.51, p < 0.004) whereby males had a face advantage and females a word advantage, as in previous studies. Here the word > face advantage in females was highly significant (t(1,50) = 3.64, p < 0.001), and whereas the face > word advantage in males did not reach significance (t(1,45) = 0.73), the face recognition of males was nevertheless superior to females (t(1,93) = 2.84, p < 0.006).

**Patient and Control Comparisons.** Mean standardized scores are shown in figure 1 for males and females. The five groups were compared with repeated measures MANOVA with group, sex, and memory modality as fac-

### Table 3. Means (standard deviations) for standardized memory scores

<table>
<thead>
<tr>
<th>Memory</th>
<th>Active</th>
<th>Withdrawn</th>
<th>Mixed</th>
<th>Remitted</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Word</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>0.10 (0.94)</td>
<td>-0.46 (0.86)</td>
<td>-0.81 (1.33)</td>
<td>-0.17 (1.03)</td>
<td>0.42 (0.59)</td>
</tr>
<tr>
<td>Female</td>
<td>-1.45 (1.06)</td>
<td>-1.45 (1.84)</td>
<td>-0.78 (1.43)</td>
<td>-0.02 (1.02)</td>
<td>0.05 (0.77)</td>
</tr>
<tr>
<td><strong>Face</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>-0.39 (0.82)</td>
<td>0.06 (1.10)</td>
<td>0.13 (1.01)</td>
<td>-0.13 (0.90)</td>
<td>0.52 (0.84)</td>
</tr>
<tr>
<td>Female</td>
<td>-0.61 (1.24)</td>
<td>-0.02 (1.32)</td>
<td>-0.51 (1.06)</td>
<td>0.22 (0.73)</td>
<td>0.47 (0.46)</td>
</tr>
</tbody>
</table>
Figure 1. Mean standardized word and face scores for the patient groups and controls

**Males**

- Controls
- Withdrawn
- Remitted
- Active
- Mixed

**Females**

- Controls
- Remitted
- Active
- Mixed
- Withdrawn
Figure 2. Mean standardized word and face scores for male patient groups who were drug free

 tors. Main effects of group and sex indicated both superior memory in controls over patients \( (F(4,189) = 14.20, p < 0.0001) \) and in males over females \( (F(1,189) = 5.36, p < 0.02) \). There was no interaction between group \( \times \) sex \( (F = 1.90, \text{NS}) \) so that the male advantage was seen in both patients and controls. Within-subject comparisons disclosed a main effect of memory modality in the direction of a word memory advantage \( (F(1,189) = 5.53, p < 0.02) \). There was also an interaction between group and memory modality \( (F(4,189) = 4.49, p < 0.002) \) and a further interaction with sex \( (F(4,189) = 5.61, p < 0.0001) \). These interactions were elucidated with repeated measures MANOVAs comparing each patient group separately with the controls and followed by \( t \) tests for dependent and independent samples as appropriate. In all comparisons, including the one with the remitted patients, there was a highly significant memory advantage in controls over patients: active \( (F(1,115) = 42.68, p < 0.0001) \), withdrawn \( (F(1,107) = 19.39, p < 0.0001) \), mixed \( (F(1,123) = 40.86, p < 0.0001) \), and remitted \( (F(1,123) = 19.39, p < 0.001) \). These effects are not repeated in the following sections addressing the interactions.

Active patients and controls. The same highly significant three-way interaction between group, sex, and memory modality \( (F(1,115) = 16.85, p < 0.0001) \) was disclosed as found in the total patient sample. Both male and female active syndrome patients had cognitive asymmetry patterns opposite to normal males and females. As hypothesized, male active syndrome patients had a significant word advantage \( (t(16) = 3.09, p < 0.007) \) that contrasted with the face advantage in male controls, whereas active syndrome females had a face advantage \( (t = 1.27) \) that contrasted with the highly significant \( (p < 0.001) \) word advantage of control females.

Withdrawn patients and controls. As in the comparison with the total patient sample, there were interactions between group and modality \( (F(1,107) = 18.81, p < 0.0001) \) and between group, sex, and memory modality \( (F(1,107) = 7.97, p < 0.006) \). As can be seen in figure 1, patients of both sexes had the hypothesized face advantage \( (\text{males}: t(11) = 3.29, p < 0.008; \text{females} t(4) = 3.32, p < 0.029) \). In females, this represented a reversal of the female word advantage found in controls.

Mixed syndrome patients and controls. There was a highly significant sex \( \times \) memory modality interaction \( (F(1,123) = 72.36, p < 0.0001) \), which indicated that the mixed syndrome patients shared the female-word/male-face memory advantages seen in controls.

Remitted patients and controls. The female word advantage and the male face advantage tended to be com-
to both groups (sex × memory modality: \( F(1,123) = 3.46, p < 0.065 \)). However, the male memory superiority in controls contrasted with a female advantage in patients (group × sex: \( F(1,123) = 3.72, p < 0.056 \)).

Summary of patient/control differences. Patient/control differences can be summarized as follows:

1. Controls had superior memory to patients, including patients whose symptoms were in remission.
2. Controls showed the previously found sex dimorphism in cognitive asymmetry in the direction of a word advantage in females and a face advantage in males, and although the latter did not reach significance, the face memory of males was nevertheless superior to the face memory of females.
3. Male subjects had superior recognition memory over females, except for patients in remission where females were at an advantage.
4. The normal male face > word advantage was notably absent in male active syndrome patients, who as hypothesized showed a word memory advantage.
5. The absence of a word advantage in female active syndrome patients distinguished them from both female controls and active syndrome males.
6. Both male and female withdrawn syndrome patients showed the hypothesized face memory advantages; in females this was a notable departure from the normal female word advantage.
7. The normal sexually dimorphic asymmetries were nevertheless present in the mixed syndrome group and in the remitted group.

Thus, with the exception of active females, active and withdrawn syndrome patients showed the hypothesized abnormal syndrome-dependent cognitive asymmetries. In active syndrome patients and withdrawn syndrome females, these asymmetries moderated the sexually dimorphic cognitive asymmetries found in normals. These differences in cognitive asymmetry were observed at through syndrome/control comparisons were then tested by comparing the patient syndromes with one another.

Psychotic Syndrome Differences. The MANOVA with factors as above was repeated including the three inpatient active, withdrawn, and mixed syndrome groups. There was no group effect, which indicates that there were no differences overall in memory ability among the syndromes. There was a main effect of sex such that the memory of female patients was poorer overall (\( F(1,66) = 4.09, p < 0.05 \)) and a main effect of memory modality such that memory for words was poorer than memory for faces (\( F(1,66) = 10.00, p < 0.05 \)). However, in line with expectations, these effects were moderated by a highly significant three-way interaction among syndrome, sex, and memory modality (\( F(2,66) = 7.63, p < 0.001 \)). This interaction was elucidated as follows.

First, pairwise comparisons between syndromes were done to examine differences in cognitive asymmetry within sexes. These confirmed that the a priori predictions of opposite cognitive asymmetry patterns in active and withdrawn syndromes held in males: Active males had higher word than face scores (\( T(16) = 3.09, p < 0.007 \)), while withdrawn males showed higher face than word scores (\( T(10) = 3.29, p < 0.008 \)). By contrast, for females only withdrawn females showed a significant asymmetry in the direction of a face advantage (\( T(4) = 3.32, p < 0.029 \)).

Second, separate MANOVAs on each syndrome were performed to examine sex differences within syndrome. In the active syndrome, females had poorer memory than males (sex = \( F(1,122) = 5.95, p < 0.023 \)) and there was an interaction between sex and memory modality (\( F(1,22) = 7.62, p < 0.01 \)). Separate examination of word and face memory scores confirmed that the word memory of active syndrome females was substantively poorer than that of their male counterparts (\( T(22) = 3.52, p < 0.002 \)). This underpinned the face > word pattern of active females, which was the opposite to word > face pattern of active males. In the withdrawn syndrome, the strong face memory advantage (\( F(1,14) = 28.27, p < 0.0001 \)) was greater in females than in males (\( F(1,14) = 6.09, p < 0.027 \)). The mixed syndrome disclosed the same sex × memory modality interaction found in controls (\( F(1,30) = 4.43, p < 0.04 \)), with a significant face advantage in males (\( T(19) = 2.69, p < 0.014 \)) but a nonsignificant word advantage in females (\( T(11) = 0.67 \)).

Summary of psychotic syndrome differences. The impressions given by control/syndrome comparisons of syndrome differences were confirmed as follows:

1. Male active and withdrawn syndrome patients disclosed opposite asymmetry patterns in support of a priori predictions: an impairment in memory for faces in the active syndrome and an impairment in memory for words in the withdrawn syndrome.
2. Female active syndrome patients showed a major departure from the results of their male counterparts (and of control females). They had a significant word memory impairment when compared with males.
3. Female withdrawn syndrome patients showed the same face > word advantage as withdrawn syndrome males (and the opposite asymmetry to female controls). The abnormal face advantage in females was actually more significant than in males.
4. The mixed syndrome had a face > word asymmetry pattern (reliable in males), as was seen in withdrawn males (and control males).
5. The recognition memory of male inpatients was superior to females, but syndrome analyses indicated that only in the active syndrome was this sex difference significant, and this was attributed to the inferior word memory of active syndrome females.

**Symptom Remission.** MANOVA comparisons of memory scores, shown in table 3, were made between the remitted group and each of the syndromes with sex as a factor. There were main effects in support of superior memory in remitted patients in comparisons with both the active syndrome \(F(1,52) = 6.63, p < 0.013\) and the mixed syndrome \(F(1,60) = 5.44, p < 0.023\). In the withdrawn syndrome there was no group effect (group: \(F(1,46) = 1.45, NS\), but there was an interaction between group and memory modality \(F(1,46) = 8.58, p < 0.005\); only the word memory of withdrawn patients was inferior to that of remitted patients \(T(46) = 2.59, p < 0.013\). Between the active syndrome and the remitted patients there was an interaction between group, sex, and memory modality \(F(1,52) = 5.66, p < 0.02\). Separate analyses for each sex indicated that the memory impairment in psychotic patients was particularly evident in the word memory of female active patients \(F(1,18) = 14.75, p < 0.001\).

**Medication.** Sufficient male patients were free of neuroleptics to examine the relationships between syndrome and cognitive asymmetry uncontaminated by antipsychotic drugs. Standardized scores are shown in figure 2. The asymmetry patterns are the same as those in figure 1. In a MANOVA comparing syndrome (active vs. mixed/withdrawn) with memory modality, there was a significant syndrome \(\times\) memory modality interaction \(F(1,12) = 6.97, p < 0.02\): a face memory impairment in the active syndrome \(\bar{t}(5) = 4.84, p < 0.005\) and a tendency toward a word memory impairment in the mixed/withdrawn syndrome \(\bar{t}(6) = 2.02, p < 0.09\). Thus, asymmetry patterns of the unmedicated patients manifested essentially the same syndrome relations as found in the total sample.

Nevertheless, correlations of memory scores with neuroleptic dose disclosed a significant correlation between high doses and poor memory for words. This finding could indicate possible drug influences on word memory or simply that patients with the poorer verbal memory were perceived to be in need of more medication. In addition, two significant trends were found when the 20 percent of patients on the anticholinergic drug procyclidine were compared with the other patients. There was a tendency toward poorer memory overall in males on the drug \(F(1,61) = 3.82, p < 0.055\) and a tendency toward poorer word memory in females on the drug \(F(1,32) = 3.81, p < 0.06\).

**Factor Analysis.** Two factor analyses (SPSS with varimax rotation and eigenvalues > 1) were carried out on the cognitive variables in combination with the clinical ratings of the psychotic patients (active, withdrawn, and mixed). In the first analysis, the discrepancy score between word and face memory was combined with the reading test (NART), which was a premorbid IQ estimate, and the ratings of positive symptom, negative symptom, and delusion scores. There were two factors. The first depicted a syndrome-asymmetry factor and accounted for 40.2 percent of the variance; the word > face asymmetry \((0.56)\) was positively associated with both the active subscales of positive symptoms \((0.78)\) and delusions \((0.73)\), and negatively associated with the withdrawn symptom score \((-0.72)\). The second factor \((22.8\%\) of the variance\) consisted of the NART \((0.87\%)\) and the discrepancy score \((0.37\%)\); this represented a verbal factor (the word advantage and the reading test).

In a second factor analysis, the word-face discrepancy score was replaced by the word and face scores. There were two factors with eigenvalues > 1 that accounted for 62.2 percent of the variance. The first was a positive/negative symptom factor accounting for 32.9 percent of the variance: negative symptoms \((-0.81)\), delusions \((0.79)\), positive symptoms \((0.75)\); the second was a cognitive general ability factor accounting for 29.3 percent of the variance: words \((0.83)\), faces \((0.78)\), NART \((0.69)\).

**Comment**

**Memory Deficits in Schizophrenia.** Memory deficits have not always been acknowledged in schizophrenia (Cutting 1990). Here the poorer memory of patients compared with controls is in agreement with what is now substantive evidence of impairments in memory processes (e.g., Calev et al. 1983; Gruzelier et al. 1988; McKenna et al. 1990; Saykin et al. 1991, 1994; Gold et al. 1994). Our evidence of recognition memory impairment included schizophrenia patients whose symptoms were in remission, although the deficit was not of the same order as found in the psychotic groups. This may suggest an improvement in memory functions with symptom recovery, and, if so, as far as recognition memory is concerned, indicates that memory impairment does not solely represent a fixed deficit. This was in fact confirmed in a further report devoted to longitudinal assessments that included tests of the same patients, with order counterbalanced, when they were psychotic and when they had recovered (Gruzelier 1999a).

Non-specific factors such as motivation, attention, distraction, and cooperation can interfere with performance.
on psychological tasks of schizophrenia patients compared with normal controls. Here there was no overt evidence of such deleterious influences in the patients examined, after the exclusion of the 12 patients with chance performance levels; conceivably the patients who were excluded may also have had severe memory difficulties masked by the extraneous factors mentioned. While these factors cannot be excluded altogether in interpreting performance differences between patients and controls, they do not confound the primary aims of the investigation, which were to determine, first, whether schizophrenia patients would disclose patterns of differential deficit in recognition memory and, second, whether these patterns were related to syndrome.

Differential Memory Deficits in Schizophrenia. Clear evidence was presented of patterned deficit. This combines with other evidence of the ability to delineate differential deficits in subgroups of schizophrenia (Lewine et al. 1997), but more pertinently it supports previous evidence of patterned deficit in learning and memory processes in active and withdrawn schizophrenia subgroups (Gruzelier et al. 1988). At the same time, there was some limited evidence of a coexisting generalized deficit, as had also been found previously in the earlier study. The deficits in the memory tests were highly correlated in both the total group of patients \((r = 0.46, p < 0.001)\) and in the psychotic group \((r = 0.51, p < 0.01)\). Factor analysis also disclosed a general cognitive factor; nevertheless, the patterned asymmetry-related deficit accounted for a substantive 40.2 percent of the variance.

Of methodological importance to the delineation of patterned deficits was the equivalence of the structure of word and face memory tasks and thereby the requirements for concentration, motivation, attention, and motor performance. Even so, the tests differed in difficulty level, a condition that led to the use of standardized scores. The pattern of results obtained, however, did not indicate that this was a critical contributing factor; the greater deficits were in word recognition, the easier of the two tasks. The reason for the difference in level of difficulty may be due to the familiarity of words and the unfamiliarity of the faces, or perhaps there is greater difficulty in encoding faces than words (see Burgess and Gruzelier, submitted).

The pattern of memory performance provided evidence of deficits in both verbal and visual recognition memory. In relation to the less frequent reports of visual memory deficits in schizophrenia, we note that without the syndrome analysis our results would have been dominated by the verbal deficit. The significant memory modality main effect in the MANOVA was in favor of a word deficit that masked the face memory deficit in a subgroup. This was also the case in our previous report of verbal and nonverbal learning and memory deficits in schizophrenia (Gruzelier et al. 1988). Here, the magnitude of the visual and verbal deficits could be seen to be of a similar order when syndrome was taken into account, and provided no evidence of a greater verbal than visual recognition memory deficit.

Syndrome Relations. The patterned deficits were not random, which would signify unspecified heterogeneity, but were related to individual differences associated with active and withdrawn syndromes. The a priori hypotheses of a face memory impairment in the active syndrome and a word memory impairment in the withdrawn syndrome held for the male patients. Thus, in male patients with an active syndrome, the influence of syndrome on asymmetry compromised the sex-related cognitive asymmetry seen repeatedly in normal subjects (Gruzelier 1994) and in the withdrawn syndrome males in whom there was a face memory advantage. In the majority of female patients, the sexually dimorphic word advantage was lost and the male face advantage was shared. In fact, the withdrawn syndrome females were characterized by a relatively severe word memory deficit, one that contributed significantly to the poorer overall memory in female than in male patients.

The results in males and withdrawn females have a counterpart in complementary evidence in active and withdrawn schizotypy traits. There, a word/face advantage was associated with an active action-oriented trait, and the opposite face/word advantage was associated with the withdrawn trait (Gruzelier and Richardson 1994; Gruzelier et al. 1995; Gruzelier and Doig 1996). Together these findings indicate that activity–withdrawal offers an important individual difference that may unravel some of the heterogeneity of findings in schizophrenic cognition and early sensory processing (Gruzelier 1999a, 1999b, 1999c).

Evidence of Left and Right Hemisphere Deficits. Aside from features of structural equivalence, the word and face recognition memory tests had fulfilled the essential requirement for localization of laterized functions, namely double dissociation between the left- and right-sided functions in the neurological validation sample (Warrington 1984). Validation of the same and similar tests has since included electrophysiological evidence (Halgren et al. 1994; Burgess and Gruzelier 1997, submitted). Given that this study fulfills this criterion and other important methodological criteria mentioned above, greater credence can be given to the findings of preferential hemispheric impairment associated with active versus withdrawn psychotic episodes (active syndrome females excepted). The criteria were only partially met in the previous investigation with neuropsychological tests of learn-
The patterns of cognitive asymmetry in recognition memory join earlier neuropsychological and psychophysiological evidence of opposite asymmetry patterns in active and withdrawn syndromes. Measures have included tests of learning and memory, including Hebb's recurring digit span test and Corsi's recurring block span test, and tests of verbal and nonverbal conditional associate memory (Gruzelier et al. 1988); electrodermal orienting response asymmetries (Gruzelier and Manchanda 1982; Gruzelier et al. 1998); an EEG spectrum analysis of stimulus intensity relations in visual evoked responses (Gruzelier et al. 1993); and P300 asymmetry (Gruzelier et al. accepted for publication). Beyond these findings is considerable evidence in the field of lateralization research that more than one asymmetry pattern does exist in schizophrenia; such evidence is marshalled across a range of measurement domains (Gruzelier 1983, 1991, 1996a, 1999a). The alignment between the left > right functional imbalance and a positive syndrome and between the right > left imbalance and a negative syndrome is also congruent with a neuropsychological translation of many aspects of positive versus negative symptomatology (Gruzelier 1983, 1984, 1991; Gruzelier et al. 1988). This is particularly the case when placed in the context of hemispheric specialization models based on reward systems that influence social interaction versus withdrawal (Tucker and Williamson 1984; Davidson and Tomarken 1989).

Sex Differences. On average, female psychotic patients had poorer memory than males, notably those in the active and withdrawn groups. Considerations such as the later onset of psychosis in female patients and their superior prognosis may give the impression that female patients have cognitive performance superior to males. One neuropsychological study has failed to support this conclusion and, without considering syndrome differences, found no sex differences (Goldberg et al. 1995). Here, the word memory impairment of the active syndrome females was a substantive contribution to the evidence of poorer memory in female patients. This represents an opposite asymmetry pattern to the one found in active males and may reflect a difference in language organization in females. The asymmetries in active and withdrawn females were highly significant but require replication for the purpose of generality.

The replicable female word > face superiority and the male face > word superiority that we have found in normal subjects (Gruzelier 1994) was seen here in the sex × memory modality interactions in the controls as well as in the mixed syndrome and remitted patient groups. These relations were absent in both the active and withdrawn syndromes, where the temperament-based imbalances in hemispheric functions appear to be a dominant influence on memory. The fact that the reversal of the sexually dimorphic asymmetries in active males and withdrawn females was shared by normal males with high femininity scores and normal females with high masculinity scores (Gruzelier 1994) may further implicate the influence of sex-related factors on cognitive asymmetry.

Medication. The evidence of syndrome-related asymmetry patterns was not invalidated by neuroleptics. Enough patients were unmedicated to indicate that they shared the same syndrome relations shown by the group as a whole (compare figures 1 and 2). Nevertheless, correlations between memory and neuroleptic dose did indicate some relationship with recognition memory for words. This finding may signify drug influences on memory or it may indicate that the patients with poorer verbal memory were prescribed higher doses of neuroleptic. If the latter is true, it would have salience for the female active syndrome patients who had the more severe word memory deficit. Neuroleptics may have contributed to the unreliable asymmetry pattern in this group. Similarly, there was a tendency for memory to be poorer in patients on anticholinergic medication. Interpretation of the medication effects requires controlled longitudinal investigation.

Conclusion. The comparison between lateralized modalities of recognition memory support earlier neuropsychological and psychophysiological findings of both left and right preferential hemispheric impairment in schizophrenia. Few investigators of lateralized abnormalities in schizophrenia have entertained the possibility of opposite patterns of asymmetry in schizophrenia. Here the patterns of asymmetry would not have been disclosed if patients had not been subdivided by syndrome. Examination of patients who presented with the same syndrome in different episodes has shown the asymmetry patterns to be reliable (Gruzelier 1999a). Our strategy of focusing on dispersion of asymmetry may help unravel some of the heterogeneity in the cognitive neuroscience of schizophrenia, including investigations of structural asymmetry where evidence of "symmetry" may mask opposite patterns of "asymmetry" (Gruzelier 1999a, 1999b).

The superior memory of patients whose symptoms were in remission, as well as evidence of reversals in asymmetry with changes of syndrome, suggests a functional component to the recognition memory impairment. The hypothesized functional basis to the memory disorder was confirmed through longitudinal investigation of patients in episodes of psychosis and recovery, as well as of patients who changed in their presenting syndrome in
different episodes (Gruzelier et al. in press). With recovery, reversals of asymmetry were found in opposite directions in the active and withdrawn syndromes. The dynamic, functional nature of the illness tends to be overlooked in the quest for neuropsychological sequelae of structural abnormalities.

Finally, the use of syndrome classification based on activity–withdrawal is further vindicated by the results of this investigation. The concepts of activity and withdrawal were once considered of central importance to schizophrenia (Wing and Brown 1970; Depue 1976), but have been neglected largely through focus on symptoms supposedly specific to schizophrenia. A return to functional considerations, such as how an illness is triggered or exacerbated and then moderated, and their consequences for brain function are long overdue. The earlier research on the significance of activity-withdrawal for individual differences in susceptibility to stress and to breakdown, and therapeutic intervention is germane to functional concerns. Elsewhere, these issues have been placed in the historical and contemporary neuroscientific context (Gruzelier 1999a, 1999b, 1999c), where it was concluded that activity and withdrawal are central to the schizophrenic process and fundamental to functional asymmetry in animals and man.

References


Gruzelier, J.; Green, J.; and Nagy, A. Differentiation in schizophrenia of orbito-frontal from dorsolateral functions in relation to bilateral electrodermal responses and syndromes. *Schizophrenia Research*. Accepted for publication.


Acknowledgments

This research was supported in part by the Wellcome Trust and SANE (Schizophrenia — A National Emergency). The authors thank C. Adams, H. Adshead, S. Cheema, P. Dennis, G. Duffield, J. Evans, S. Hirsch, C. Hutchings, K. Laws, D. Rhatigan, and S. Spence for assistance and support.

The Authors

John H. Gruzelier, M.A., Ph.D., is Professor of Psychology; Lesley Wilson, M.R.C.Psych., and Lillian Pusavat, M.R.C.Psych., are Consultant Psychiatrists; and David Liddiard, B.Sc., is Senior Psychologist, Department of Behavioral and Cognitive Sciences, Imperial College School of Medicine, Charing Cross Hospital, London, England. Emmanuelle Peters, Ph.D., is Lecturer, Department of Psychology, University College of London, London, England.