Are Gender Differences in Schizophrenia Reflected in Brain Event-Related Potentials?

by Richard C. Josiassen, Richard A. Roemer, Michele M. Johnson, and Charles Shagass

Abstract

Numerous studies have reported relationships between gender and cerebral event-related potentials (ERPs) recorded from the human scalp. Recent studies have suggested that the influences of gender on ERPs may differ in persons with schizophrenia compared to healthy controls. In a further evaluation of the influences of this critical subject variable on ERP characteristics in schizophrenia, ERPs of age- and gender-matched groups (n = 72 each) of unmedicated schizophrenic patients and healthy controls were compared. ERPs elicited by left and right median nerve stimulation, checkerboard pattern visual flash, and auditory clicks were recorded from 15 scalp leads. The results confirm previous findings showing that: (1) number of comparable gender effects present in the ERP records of these two large study groups and (2) specific Diagnosis x Gender interactions suggesting that schizophrenic illness may modify normal gender influences on ERP characteristics. These data illustrate the point that matching schizophrenic patients and healthy control populations for gender is essential but not sufficient. Even in carefully matched groups, gender confounding can persist as a source of error variance because the influence can vary for different diagnostic groups.

For nearly a quarter of a century, gender differences have been noted in cerebral event-related potentials (ERPs) recorded from the human scalp. Gender differences were observed in the visual modality by Rodin et al. (1965) who found higher amplitudes and shorter latencies in females than in males. Similar results were reported by Shagass and Schwartz (1965b). Using the pattern-shift visual ERP method, Stockard et al. (1979) and Kjaer (1980) found shorter latencies in females than in males, although Kjaer reported this trend was age dependent (females had longer latencies than males in the 10- to 19-year age range). In the auditory modality, there is general agreement that females have shorter absolute and interpeak latencies on very early brainstem components (Beagley and Sheldrake 1978), although there do not appear to be significant gender differences in premature infants, newborns, and young children (McClelland and McCrea 1979). Somatosensory studies using stimuli to the upper extremities have found amplitudes, during the first 100 ms, to be higher and the latencies of peaks to be shorter in women (Shagass and Schwartz 1965a; Ikuta and Furuta 1982; Allison et al. 1983; Mervaala et al. 1988). Kakigi (1987), stimulating the posterior tibial nerve, found females to have higher amplitude somatosensory evoked potentials. However, there were few latency differences between the sexes in younger subjects, longer interpeak latencies in 60- to 74-year-old females than in males, and inconsistent gender effects in those over 75 years old.

The notion that ERP characteristics may in certain respects be sexually differentiated is not surprising in view of the influence of sex hormones on brain development and subsequent neurochemical processes. Sexual dimorphism can be

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demonstrated in a wide variety of parameters that could influence overall ERP profiles, such as volumes of certain brain regions, the size and number of specific cells, the extent of dendritic and axonal branching and synapse formation, the activity of neurotransmitter systems, and the density of steroid receptors in several brain areas (DeVries et al. 1984). Stockard et al. (1979) have speculated that head size and deep body temperature may be contributing factors, whereas Fleck and Polich (1988) have examined influences of the menstrual cycle. Although this scattered literature is in need of refined and systematic investigation, the data consistently point to gender as a critical subject variable in ERP investigation.

Gender-related ERP differences also have been noted in studies of schizophrenia (Shagass and Schwartz 1963, 1965a, 1965b; Shagass et al. 1972; Buchsbaum et al. 1974; Hegerl et al. 1988; Jøsiiassen et al. 1988a). It is not readily apparent, however, whether all the gender effects observed in schizophrenia are comparable to those observed in healthy controls. Indeed, there is some sparse evidence suggesting that the gender-related ERP effects seen in healthy populations may be modified in psychiatric illness. In a recent set of ERP comparisons using large study groups with subjects individually matched for age and gender (schizophrenic patients vs. healthy adults, n = 129 in each group; schizophrenic vs. major depressive patients, n = 74 in each group), Jøsiiassen et al. (1988a) used a multifactorial analysis of variance (ANOVA) to examine the ERP data (Diagnosis, Age, and Gender entered as main effects). As expected, significant main effects were observed for Diagnosis, Age, and Gender, but, surprisingly, several highly significant interactions emerged between Diagnosis and Gender. One of these Diagnosis x Gender interactions is illustrative. Figure 1 displays group values taken from the schizophrenia versus major depression comparison. The three-way ANOVA results for this one auditory ERP measurement indicated that mean factor score values were higher for depressed patients than for schizophrenic patients (Diagnosis effect, p < 0.001) and higher for women than for men.
(Gender effect, p < 0.009). When gender was partitioned by diagnostic group (Diagnosis x Gender interaction, p < 0.03), however, the pattern of higher values among women was seen for the major depressive patients but was not present in the schizophrenic patients. Moreover, the significant diagnostic difference seen for this auditory factor actually was limited to females and would not have been significant in a comparison of males only. A further example is found in the study of Buchsbaum et al. (1973); they measured the relationship between visual ERP amplitude and flash intensity (augmenting-reducing) using depressed patients and healthy control subjects. The visual ERP amplitudes (for components P100–N140) increased with increasing flash intensity (augmenting) in both male and female bipolar depressed patients; however, among healthy controls, this kind of intensity curve was present only in male subjects, with a nearly flat intensity curve among female controls. In this same vein, Gur et al. (1985) compared regional cerebral blood flow (rCBF) measurements from 19 unmedicated schizophrenic patients and 19 age- and gender-matched healthy control subjects, and also reported significant Diagnosis x Gender interactions in activated rCBF measures. Such observations raise the possibility that gender effects on functional brain measures can vary across diagnostic groups and reflect influences beyond the sexually dimorphic nature of the human brain.

The present exploratory study focuses on gender-related ERP effects in unmedicated schizophrenic patients. It examines two specific issues: (1) ERP data are presented that demonstrate gender effects in two relatively large study groups—unmedicated schizophrenic patients and healthy control subjects individually matched for age and gender (n = 72 each). (2) The same data are used to explore specific Diagnosis x Gender interactions which suggest that schizophrenic illness may modify normal gender influences on ERP characteristics. The present data provide evidence that both types of gender-related ERP influences are present (e.g., main Gender effects and Gender x Diagnosis interactions), and lend support to the trend toward more detailed consideration of the sexually dimorphic nature of the brain and the possibility of illness-related modifications.

Methods

Subjects. The 72 unmedicated schizophrenic and 72 healthy control subjects in this retrospective study were drawn from an available pool of archived ERP records for 839 adult subjects.1 Within this data set are ERP records from 171 schizophrenic patients (105 males and 66 females), 96 of whom were unmedicated at the time of the ERP testing, along with ERP records from 195 healthy controls (96 males and 99 females). Schizophrenic patients were selected for study if they were unmedicated and could be individually matched for gender and age (within 4 years) with a healthy control to give two equal-sized comparison groups. The 72 patients used in this study were free of medication for a median of 10 days (at least 3 days, but more than 6 days in nearly all cases). Table 1 gives descriptive information about the subject groups.

Diagnoses were based on hospital chart review following discharge and were done independently by two senior psychiatrists. In addition, the Research Diagnostic Criteria (RDC) of Feighner et al. (1972) were applied to relevant diagnostic categories; the RDC of Spitzer et al. (1978) were applied for schizoaffective disorders. All subjects were screened by interview before their participation, with the following exclusionary criteria: (1) history of antecedent neurological or craniocerebral trauma; (2) evidence of sensory loss, peripheral nerve damage, or disorders of skin sensation; (3) diabetes or seizure disorder; (4) pregnancy; and (5) recent or extensive alcohol or drug abuse. All healthy controls were further screened for use of centrally active medication and psychiatric impairment.

Gender Differences in Clinical Expression. The question of gender differences in the clinical expression of schizophrenia is pertinent to the present study. Table 2 summarizes available clinical data on the 38 females and 34 males who made up the group of 72 unmedicated schizophrenic patients in the sample. The clinical data include intellectual functioning (Raven 1960), duration of illness, number of hospitalizations, days drug free, and clinical observations using the Brief Psychiatric Rating Scale (BPRS; Overall and Gorham 1962). The results of univariate t-test comparisons are indicated. The overall
Table 1. Description of subjects

<table>
<thead>
<tr>
<th>Diagnosis1</th>
<th>Age (years)</th>
<th>Range</th>
<th>Mean</th>
<th>Male/Female</th>
<th>RDC2</th>
<th>DDF3</th>
<th>Duration of Illness4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizophrenia (n = 72)</td>
<td>17-56</td>
<td>24.5</td>
<td>34/38</td>
<td>57/72</td>
<td>10 (3-99)</td>
<td>45 (1-276)</td>
<td></td>
</tr>
<tr>
<td>Healthy control (n = 72)</td>
<td>14-56</td>
<td>25.0</td>
<td>34/38</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

1 Diagnostic subtypes were as follows: chronic paranoid (15), chronic undifferentiated (24), schizoaffective (15), schizoaffective disorder (11), atypical psychosis (1), catatonic (4), simple (1), and brief reactive psychosis (1).
2 RDC = Research Diagnostic Criteria. Feighner or Spitzer RDC, of subjects meeting definite or probable level. RDC not applicable to schizoaffective, brief reactive psychosis, simple, or atypical psychosis. Thus, where applicable, the actual number of schizophrenic patients meeting RDC was 57/58 (98.3%).
3 DDF = days drug free. Median refers to number of documented days off medication; duration, if longer than 99 days, is coded as 99.
4 Duration of illness = estimate of total months since first episode of illness.

BPRS scores between groups were compared using Hotelling’s T² (Morrison 1967) and were not significant (F value = 1.33; df = 16,55; p > 0.20).

Recording Procedures. The subject sat in a comfortable chair in an electrically shielded, dimly lit room with earphones in place. The subject was asked to look continually at a constantly illuminated fixation point on a television screen while four types of stimuli were presented in a pseudorandom order. The recording procedures have been described previously (Shagass et al. 1977; Josiassen et al. 1988a), and only selected details are given below.

Stimuli. Somatosensory stimuli consisted of 0.1-ms electrical pulses, generated by a constant current source, and delivered to the right or left median nerves at the wrist through disks affixed with collodion. Because one stimulator served both wrists, the intensity used was 10 mA above the mean of the two sensory thresholds (stimulating leads were reapplied if the difference between the two thresholds was > 1 mA. Visual stimuli consisted of the 8-ms presentation of a checkerboard pattern on a television monitor placed 4 feet from the subject’s eyes. The checkerboard pattern was composed of two 19 x 19 cm squares separated by an 0.7 cm vertical dark strip, the center of which contained the fixation point. Each square contained 128 black and 128 white checks. The mean intensity of the checkerboard was 1.2 foot lambert. Auditory stimuli were 0.1-ms binaural clicks, presented to both ears through earphones. To minimize the effect of ambient room noise, a constant level of white noise at 75 dB was introduced into the earphones; the actual click level was 125 dB (i.e., 50 dB above the white noise level). These four types of stimuli (left somatosensory, right somatosensory, visual, and auditory) were presented in a pseudorandom order, with the constraints that no two identical stimuli should be delivered in succession and that an equal number of each kind of stimulus should be delivered within any block of 192 stimuli. The interval between successive stimuli was randomized between 1.5 and 2.0 seconds with a mean of 1.75 seconds.

Electrodes. Stimulating and recording electrodes for the electroencephalogram (EEG) were chlorided silver disks. All scalp leads were affixed with electroencephalographic (EEG) paste, with scalp impedance level maintained at 5 kΩ or below. Recordings were taken from 15 leads that were, with exceptions, placed according to the 10-20 International System (Jasper 1958). The standard leads included T3, T4, T5, T6, O2, O1, Oz, Cz. Nonstandard recording leads were F3X, F4X, C3X, and C4X (placed 2 cm posterior and 1 cm lateral to the standard F3, F4, C3, and C4 locations), and O3 and O4 (placed midway between T5 and O1 and T6 and O2). Scalp leads were referenced to the ears (A1 and A2) linked through 22 kΩ resistors. The lead designated electrooculogram (EOG) was placed midline near the nasion to monitor the EOG. Somatosensory stimulating leads were placed 3 cm apart over the median nerve at the wrist, anode distal.

Recording. Averaging of 192 EEG samples for each kind of stimulus was performed online by a parallel distributed processing (PDP-12) computer (512-ms analysis time, 1-ms sampling interval sequentially multiplexed with 20μs between channels). Amplifier frequency cutoff was 3 KHz and the time constant was 0.45 seconds. The stimulus was delayed by 10 percent of the computer trace, and a 10μV calibration signal was entered in series with the recording electrodes during the prestimulus interval. The EEG was monitored by an artifact detector during each stimulus...
Table 2. Description of clinical expression

<table>
<thead>
<tr>
<th></th>
<th>Schizophrenic males (n = 34)</th>
<th>Schizophrenic females (n = 38)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raven percentiles, mean (SD)</td>
<td>43.1 (32.2)</td>
<td>33.7 (28.9)</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of illness (months)</td>
<td>61.0</td>
<td>63.7</td>
<td>NS</td>
</tr>
<tr>
<td>No. of hospitalizations</td>
<td>3.9</td>
<td>4.1</td>
<td>NS</td>
</tr>
<tr>
<td>Days drug free</td>
<td>13.4</td>
<td>10.4</td>
<td>NS</td>
</tr>
<tr>
<td>Brief Psychiatric Rating Scales</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somatic Concern</td>
<td>0.62</td>
<td>1.47</td>
<td>&lt; 0.02</td>
</tr>
<tr>
<td>Anxiety</td>
<td>1.26</td>
<td>1.39</td>
<td>NS</td>
</tr>
<tr>
<td>Emotional Withdrawal</td>
<td>2.32</td>
<td>1.50</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Conceptual Disorganization</td>
<td>1.91</td>
<td>0.92</td>
<td>&lt; 0.006</td>
</tr>
<tr>
<td>Guilt Feelings</td>
<td>0.12</td>
<td>0.21</td>
<td>NS</td>
</tr>
<tr>
<td>Tension</td>
<td>1.82</td>
<td>1.53</td>
<td>NS</td>
</tr>
<tr>
<td>Mannerisms &amp; Posturing</td>
<td>0.79</td>
<td>0.63</td>
<td>NS</td>
</tr>
<tr>
<td>Grandiosity</td>
<td>0.44</td>
<td>0.26</td>
<td>NS</td>
</tr>
<tr>
<td>Depressive Mood</td>
<td>0.59</td>
<td>0.74</td>
<td>NS</td>
</tr>
<tr>
<td>Hostility</td>
<td>0.97</td>
<td>1.32</td>
<td>NS</td>
</tr>
<tr>
<td>Suspiciousness</td>
<td>1.97</td>
<td>2.13</td>
<td>NS</td>
</tr>
<tr>
<td>Hallucinatory Behavior</td>
<td>1.47</td>
<td>1.08</td>
<td>NS</td>
</tr>
<tr>
<td>Motor Retardation</td>
<td>1.00</td>
<td>0.74</td>
<td>NS</td>
</tr>
<tr>
<td>Uncooperativeness</td>
<td>0.97</td>
<td>1.21</td>
<td>NS</td>
</tr>
<tr>
<td>Unusual Thought Content</td>
<td>1.79</td>
<td>1.74</td>
<td>NS</td>
</tr>
<tr>
<td>Blunted Affect</td>
<td>2.00</td>
<td>1.37</td>
<td>NS</td>
</tr>
</tbody>
</table>

Note.—The Raven Progressive Matrices (Raven 1960) test was used as a self-administered measure of functional intelligence. The test was completed within 1 week of event-related potential testing, after a staff member gave instructions and ascertained that these instructions were understood. The Brief Psychiatric Rating Scale (Overall and Gorham 1962) was completed by a senior psychiatrist on the basis of a direct patient interview within 1 week of event-related potential testing.

Treatment of Data

As a visual illustration of the basic ERP phenomena, group mean ERP tracings from selected leads are displayed in figure 2. The illustration contains mean ERP's to the four kinds of stimuli used in this study for healthy control subjects and matched schizophrenic patients. These figures show the sequence of ERP components normally observed. For example, when the convention of designating components by polarity and usual peak latency was followed, the somatosensory ERP's recorded from leads thought to be placed over the primary somatosensory cortex in the postcentral gyrus (left median nerve—lead C4X; right median nerve—lead C3X) contained the following peaks: P15, N20, P30, P45, N60, P100, N130, and P180. The usual sequence of ERP events was also seen in the visual and auditory signals. Two-tailed independent t-tests were performed on all corresponding pairs of poststimulus data points (starting at 9 ms) to show the temporal points at which schizophrenic and controls group mean ERP's differed. The t test display was arranged so that it departed from baseline when the 0.05 level was achieved, with higher t values proportionally represented. There is little statistical merit in computing this large number of t tests, and for the purposes of this report the effort is solely intended as a visual aid.

Principal Component Analysis.

Selection of data values. There are many approaches available for the quantification of ERP events (Donchin and Heffley 1978). This study used principal component analysis (PCA) factor structures derived from archived ERP records of 195 healthy control subjects to develop factor scores for the entire archived set of 839 subjects (195 healthy controls and 644 psychiatric patients). These factor scores were
Figure 2. Mean event-related potentials (ERPs) from selected leads to 4 kinds of stimuli for 72 healthy controls (solid line) and 72 schizophrenic patients (broken line), matched for age and gender.

Mean ERP baseline is offset for illustration only. Lead designations are as shown in head diagram. C and F leads (C3X, F3X, etc.) are displaced 2 cm posterior and 1 cm lateral to the conventional 10-20 locations. Leads are referenced to linked ears; scalp positivity gives upward deflection. Line below each pair of tracings displays results of two-tailed t tests comparing consecutive corresponding mean data points. Line rises above horizontal when $p = 0.05$ and varies proportionally for lower $p$ values.
then used as the basic data for statistical analysis. The PCAs in this study were performed on each of the four modalities individually, using all 15 scalp recordings from the 195 healthy controls (2,925 observations or “cases” per modality). The actual PCAs were performed using Biomedical Data Package (BMDP4M) (Dixon et al. 1983) on a PDP11 computer.

Factor Structures Yielded by PCA of Healthy Control ERP Waveforms. To approach a theoretically reasonable number of observations per variable for PCA, it was decided to reduce the number of data values that represented an ERP to less than 50 values. This was accomplished by “ninthering” (Tukey 1978; Roemer et al., in press). The original ERP’s consisted of 432 data values (16-448 ms poststimulus). The medians of consecutive sets of three data values yielded a new data vector of 144 median values. The “ninther” values were the medians of three consecutive median values, yielding a 9:1 reduction of the original 432 values to a final data vector of 48 values that represented 9-ms intervals beginning at 16 ms. It should be noted that this 9:1 time compression reduced the resolution of early, more rapid ERP events and, as a result, the early portions of the ERPs (< 60 ms) are not meaningfully represented in this analysis.

The PCAs of ERPs for the total sample of 195 healthy controls yielded a total of 20 factors with BMDP4M using the covariance matrix about the origin (OACVA) option followed by varimax rotation (left somatosensory = 6 factors; right somatosensory = 6 factors; auditory = 4 factors; visual = 4 factors). Figure 3 illustrates the structures of the left and right somatosensory ERP factor basis waves, which show a high degree of similarity. Figure 4 illustrates the factor basis waves for visual and auditory ERPs. The total variance for each kind of ERP accounted for by these PCA factors ranged from 85.2 to 89.7 percent. Factor scores for both healthy control subjects and patients with schizophrenia were computed using the PCA from the controls. To represent the topographic distribution of values across the scalp, a vector of 15 factor scores was developed for each individual basis wave, or one factor score per scalp lead.

The rationale for using the healthy control population to identify underlying ERP factor structures and then to derive factor scores for the entire population from the control factor structures is based on the recent demonstration that factor structures from schizophrenic and healthy control groups represented the same factor space (Roemer et al., in press).

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The OCOVA option was selected because no transformations are performed on the data in computing the association matrix. The resultant factor basis waves retain latency and polarity characteristics that allow the factors to be compared to temporal and spatial characteristics of the original ERP records. Such relationships are not easily drawn, however, since PCAs depend on common variance within the entire data set while individual ERP records do not. The resultant factor scores reflect correct polarity and the factor loadings retain the original $\mu$V scale (Friedman et al. 1984). Procedural details for developing factor scores are presented in Roemer et al. (in press).

Statistical Comparisons of Factor Score Vectors Using ANOVA. The 72 unmedicated schizophrenic patients and their matched control subjects were compared with respect to each of the 20 sets of vectors of factor scores by ANOVA with repeated measures (BMDP2V). This ANOVA design permitted tests of: (1) main effects for Diagnosis (schizophrenic, control), Gender, Age (above and below total population median) and Leads (15 leads), and (2) all possible interactions. The Greenhouse-Geisser correction was used to determine the significance of ANOVA terms using degrees of freedom reduced by multiplication with a proportion termed the “epsilon correction” (Jennings 1987). The degrees of freedom are adjusted by the following equation: epsilon (K-1) and epsilon (K-1)(N-1) degrees of freedom for the critical F ratio. These epsilon factors are computed by BMDP2V. The epsilon factor in this study ranged from 0.2 to 0.36 with the original degrees of freedom being K = 15 and N = 144. This is considered a conservative approach for ANOVA with repeated measures. The set of conservative ANOVAs yielded a large number of main effects and interactions at the 5 percent level of significance (two-tailed). The main effects for Group, Gender, and pertinent interactions are the primary focus of this report.

Results

Results from the 20 ANOVAs comparing factor scores from unmedicated schizophrenic patients and matched healthy control subjects are selectively summarized in Table 3. Because this is an exploratory study consisting of 20 multifactorial ANOVAs on two sets of subjects...
Figure 3. Basis waves (factor structures) for “ninthered” signals of somatosensory evoked potentials to left (LSEP) and right (RSEP) median nerve stimuli applied at the wrist

Ninther Factor Structures

LSEP

RSEP

(n = 72 each), findings should be viewed with caution since one would expect that 5 percent of the effects would be statistically significant findings by chance alone. However, the likelihood that these data reflect more than chance is increased by the use of the conservative ANOVA. Individual factors are identified in the table and throughout the remainder of the report using the following abbreviations: LSF = left somatosensory factor; RSF = right somatosensory factor; VF = visual factor; and AV = auditory factor. The mean factor score values are shown for all 20 factors by Diagnosis, Gender, and Diagnosis x Gender, all collapsed across 15 scalp leads.

Diagnosis Effects and Lead x Diagnosis Interactions. In this set of 20 ANOVAs, significant Diagnosis effects indicate that overall factor score values (across the 15 scalp leads) differed in some manner between the schizophrenic and controls groups on a given factor. The main effect of Diagnosis was significant for 9 of the 20 factors: LSF2 (F = 11.3, p < 0.001), LSF3 (F = 8.45, p < 0.004), LSF6 (F = 5.00, p < 0.03), RSF1 (F = 6.86, p < 0.009), RSF2 (F = 13.3, p < 0.0004), RSF6 (F = 5.82, p < 0.02), VF2 (F = 10.5, p < 0.002), AF1 (F = 11.6, p < 0.0009), and AF4 (F = 7.61, p < 0.007).

Table 3 shows the actual mean factor score values for Diagnosis. Since the polarity of the basic ERP tracings was retained in the factor scores, it was necessary to assess the polarity of the ERP component reflected in the factor score to determine which diagnostic group had greater factor score values. For example, LSF5 corresponds in time to peak N140, which is a negative polarity component (compare LSF5 in figure 3 and
peak N140 in figure 2). Thus, a more negative factor score in table 3 (control = -0.115 vs. schizophrenic patients = 0.189) is interpreted as reflecting greater negative amplitude in control subjects relative to schizophrenic patients. This observation is in accord with previously reported ERP differences between schizophrenic patients and healthy control subjects (Shagass et al. 1977). In general, the mean values for significantly different factors were of larger amplitude for control subjects across the 15 scalp leads than for schizophrenic patients. These findings are in reassuring agreement with previous gender- and age-matched comparisons from this population (Shagass et al. 1977, 1978, 1985).

The Diagnosis (2 groups) × Lead (15 lead) interaction term evaluates group factor score differences at all scalp recording sites. This interaction was significant for 10 of the 20 factors using Greenhouse-Geisser probabilities: LSF1 (F = 3.65, p < 0.01), LSF2 (F = 8.53, p < 0.0001), LSF4 (F = 3.01, p < 0.02), LSF5 (F = 3.18, p < 0.02), RSF1 (F = 6.33, p < 0.0003), RSF2 (F = 3.80, p < 0.01), RSF4 (F = 3.02, p < 0.02), VF2 (F = 4.03, p < 0.008), VF3 (F = 4.26, p < 0.008), and AF1 (F = 7.21, p < 0.001). Since leads are taken into account, each of these significant interactions could be described topographically from the relative magnitudes of factor scores at the different scalp locations for both groups. These will not be discussed in detail. However, to illustrate one of the significant interactions (LSF2), the basic mapping program of Coppola et al. (1982), modified by the recommendations of Desmedt et al. (1987), was used to display the factor scores with interpolated values on the head diagram shown in figure 5. It can be seen that factor score values for LSF2 were larger for controls at all scalp sites, but the magnitude of the between-group differences was considerably greater at central and right
parietal recording sites. The nature of each of the 10 Diagnosis x Lead interactions was unique and would require detailed analysis that is beyond the intent of this article.

The main effect of Gender compares factor scores for males and females across all scalp recording sites without regard to diagnosis. The Gender effect was significant for 5 of the 20 factors: LSF1 (F = 4.42, p < 0.04), LSF2 (F = 5.12, p < 0.03), RSF3 (F = 5.50, p < 0.02), AF3 (F = 5.11, p < 0.03), and AF4 (F = 5.31, p < 0.02). The mean values for these significant factors can be seen in table 3, which indicates that the direction of effect varied from factor to factor. For example, LSF1 was larger in females, whereas LSF2 was larger in males.

The Lead x Gender interaction examined factor scores for males and females at individual recording sites. Interaction terms were significant for 4 of the 20 factors: LSF2 (F = 2.58, p < 0.04), VF3 (F = 4.24, p < 0.005), AF3 (F = 2.84, p < 0.05), and AF4 (F = 3.95, p < 0.009). Diagnosis x Gender and Lead x Diagnosis x Gender Interactions. To determine whether Gender effects differed between the two diagnostic groups, both the Diagnosis x Gender and the Lead x Diagnosis x Gender interaction terms were examined. The Diagnosis x Gender interaction term was significant for 3 of the 20 factors: LSF6 (F = 3.73, p < 0.05), AF1 (F = 4.35, p < 0.03), and AF3 (F = 3.96, p < 0.05). Figure 6 illustrates the mean factor score values for these significant inter-

Table 3. Mean factor scores of 72 unmedicated schizophrenic (Sz) patients and 72 healthy controls (C) matched for age and gender (collapsed across 15 scalp leads)

<table>
<thead>
<tr>
<th>Principal component analysis factors</th>
<th>Diagnoses (D)</th>
<th>Gender (G)</th>
<th>D x G interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Females (F)</td>
<td>Males (M)</td>
<td>SZF</td>
</tr>
<tr>
<td>Left somatosensory factors (LSF)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LSF1</td>
<td>0.246</td>
<td>0.355</td>
<td>0.404</td>
</tr>
<tr>
<td>LSF2</td>
<td>0.243</td>
<td>0.602</td>
<td>0.302</td>
</tr>
<tr>
<td>LSF3</td>
<td>0.141</td>
<td>0.163</td>
<td>0.249</td>
</tr>
<tr>
<td>LSF4</td>
<td>0.457</td>
<td>0.313</td>
<td>0.396</td>
</tr>
<tr>
<td>LSF5</td>
<td>0.189</td>
<td>-0.115</td>
<td>0.128</td>
</tr>
<tr>
<td>LSF6</td>
<td>0.072</td>
<td>0.250</td>
<td>0.210</td>
</tr>
<tr>
<td>Right somatosensory factors (RSF)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RSF1</td>
<td>0.271</td>
<td>0.497</td>
<td>0.451</td>
</tr>
<tr>
<td>RSF2</td>
<td>0.086</td>
<td>0.518</td>
<td>0.204</td>
</tr>
<tr>
<td>RSF3</td>
<td>0.086</td>
<td>0.131</td>
<td>0.229</td>
</tr>
<tr>
<td>RSF4</td>
<td>0.424</td>
<td>0.351</td>
<td>0.358</td>
</tr>
<tr>
<td>RSF5</td>
<td>0.036</td>
<td>-0.092</td>
<td>0.043</td>
</tr>
<tr>
<td>RSF6</td>
<td>0.093</td>
<td>0.286</td>
<td>0.218</td>
</tr>
<tr>
<td>Visual factors (VF)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VF1</td>
<td>0.302</td>
<td>0.515</td>
<td>0.468</td>
</tr>
<tr>
<td>VF2</td>
<td>0.091</td>
<td>0.437</td>
<td>0.328</td>
</tr>
<tr>
<td>VF3</td>
<td>-0.256</td>
<td>-0.253</td>
<td>-0.198</td>
</tr>
<tr>
<td>VF4</td>
<td>0.055</td>
<td>0.125</td>
<td>0.057</td>
</tr>
<tr>
<td>Auditory factors (AF)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AF1</td>
<td>0.354</td>
<td>0.655</td>
<td>0.466</td>
</tr>
<tr>
<td>AF2</td>
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<td>0.183</td>
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<tr>
<td>AF3</td>
<td>-0.082</td>
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</tr>
<tr>
<td>AF4</td>
<td>0.162</td>
<td>-0.169</td>
<td>0.135</td>
</tr>
</tbody>
</table>

*p < 0.05; each significant term is fully described in the text.
The possibility of differential Diagnosis × Gender affects being contributed by a particular cluster of recording sites was suggested in only one of the three-way interactions (Lead × Diagnosis × Gender): AF3 ($F = 3.29, p < 0.03$). Brain maps of this negative polarity factor (figure 7) illustrate the nature of this significant three-way interaction. In the female and male control subjects, (top maps), a cluster of negative values was seen in central (Cz) and bilateral frontocentral locations with positive values being obtained in posterior recording sites and the EOG. The female schizophrenic patients (bottom left map) follow a similar pattern and in many ways resemble the male control subjects. On the other hand, the brain map of the male schizophrenic patients (bottom right map) is shifted toward more positive values across all the recording sites.

**Lead Effects, Age Effects, and Lead × Age Interactions.** The main effect of Leads was highly significant in each of the 20 ANOVAs ($p < 0.0001$ in every case), whereas the main effect of Age was significant for only 1 of the 20 factors: AF4 ($F = 3.96, p < 0.05$). The Age × Lead interaction term was significant for 6 of the 20 factors. While these ANOVA terms are outside the focus of this report, it should be pointed out that these effects were tested in each analysis and, therefore, took into account that proportion of variance related to Age and Leads and the related interaction.

**Lead × Diagnosis × Gender × Age Interactions.** When the interaction of all four main effects (Lead, Diagnosis, Gender, and Age) was evaluated, 4 of the 20 factors were significant: LSF1 ($F = 3.95, p < 0.009$).
Figure 6. Mean factor score values for three significant Diagnosis × Gender (D × G) interactions

Significant Diagnosis × Gender Interactions

Curves on the left show mean values for left somatosensory factor 6 (D × G, p < 0.05); middle curves show auditory factor 1 (D × G, p < 0.03); curves on right show auditory factor 3 (D × G, p < 0.03).

LSF4 (F = 3.26, p < 0.01), RSF1 (F = 4.51, p < 0.004), and RSF4 (F = 5.74, p < 0.0003). Note that factors LSF4, RSF1, and RSF4 did not yield any prior significant main effects for Diagnosis or Gender, or a significant Diagnosis × Gender interaction (see table 3). When Age was used in the examination of interactions, however, these three factors yielded significant findings.

Discussion

The results of this study are coherent with a growing body of literature showing gender to be a critical subject variable that contributes an important fraction of variance, not only in ERP studies of schizophrenia, but also in measures of cerebral blood flow (Gur et al. 1985; Daniel et al. 1988), positron emission tomography (Baxter et al. 1987; Yoshii et al. 1988), and platelet monoamine oxidase activity (Meltzer and Zureick 1987). For 5 of the 20 factors (25%) in this study, males and females were significantly different across all scalp recording sites, with 4 of the 20 factors yielding significant Gender effects clustered at different scalp locations. Many ERP investigators have attempted to control for this recognized source of variance either by holding gender constant (e.g., using only males) or by matching comparison groups for gender.

Another aspect of this problem is noted in a recent review by Cohen (in press), who scrutinized 53 studies of cognitive ERPs in schizophrenia. Strangely enough, of the 857 schizophrenic patients reported in these studies, only 88 of the patients tested were women. This sampling bias is likely to introduce serious distortions in the literature and most certainly limits the generalizability of findings.

However, while gender may be acknowledged regularly as an important source of variability, it is often inadequately controlled in ERP studies of schizophrenic illness (Josiassen and Johnson 1988). Attention to gender matching might help to clarify puzzling inconsistencies in the various functional measures of brain activity in schizophrenia research. Even in carefully matched groups, however, gender confounding persists as a critical source of variance. In the present comparison, 11 of the 20 factors (55%) ERP factors (LSF1, LSF2, LSF4, LSF6, RSF1, RSF3, RSF4, VF3, AF1, AF3, and AF4) yielded significant main effects for Gender or interactions involving Diagnosis and Gender, and this presents several methodological problems. Clearly,
Figure 7. Brain maps showing the relative magnitude of mean factor score values from auditory factor 3 (AF3) illustrating Lead x Diagnosis x Gender interaction (p < 0.03)

Auditory Factor 3
(Lead x Diagnosis x Gender Interaction)

Female Controls (N=38)  Male Controls (N=34)
Female Schizophrenics (N=38)  Male Schizophrenics (N=34)

1.620  1.290  0.960  0.630  0.300  0.030  -0.360  -0.690  -1.020  -1.350

Top tracings show brain maps of healthy control males (n = 34) and females (n = 38). Bottom tracings show brain maps of schizophrenic males (n = 34) and females (n = 38). The range of factor score values for the 4 brain maps is displayed on the right.

The basic approach of gender matching is not sufficient. Balancing of the genders is also required since an observed diagnostic difference in unbalanced groups actually may be the statistical artifact of a Diagnosis x Gender interaction. This problem is illustrated in figure 1, where the observed diagnostic differences (main effect for Diagnosis, p < 0.001) were present only in females and would not have been identified as significant if the comparison groups had been composed primarily of males. Moreover, gender balancing alone does not obviate the need for multifactorial statistical analysis. Further problems are illustrated in the curves shown in figure 6. The LSF6 tracing illustrates a case where no significant main effects of Diagnosis or Gender were obtained, and yet the male schizophrenic patients clearly differed from female schizophrenic patients and healthy control subjects. In the case of factor AF1, a significant main effect for Diagnosis was obtained, but the Gender effects in schizophrenic patients and healthy controls were in the opposite direction. As for factor AF3, a significant main effect for Gender resulted from the fact that the schizophrenic males markedly differed from the female schizophrenic patients and healthy control groups. Thus, there could be cases, even in gender-matched and gender-balanced groups, where main effects for Diagnosis or Gender primarily result from a significant interaction that renders any interpretation of the main effects substantively meaningless. Clearly, if influence of gender is not brought under experimental or statistical control, it will continue to have the potential to bias statistical results even in those groups carefully matched and balanced for gender. Although a growing body of data points to gender-related ERP differences in patients with schizophrenia, any attempt to understand these findings beyond the methodological implications must begin by noting that gender and clinical expression of schizophrenia are interwoven. There are well-documented gender differences in age of onset, course of illness, and response to pharmacologic treatment (for reviews, see Lewine 1981; Goldstein and Link 1988). For example, the peak age of onset of schizophrenia is significantly later for women than for men (Lewine 1981; Seeman 1985). Moreover, the early onset of schizophrenia in men has generally been accompanied by poor premorbid competence and typical symptom presentation, whereas the late-onset form of schizophrenia most typical in females is often
associated with good premorbid competence and affective symptoms (Garmezy 1970). There are reports that women may have a significantly less severe course to their illness than men (Sartorius et al. 1978; Salokangas 1983), and that women may be better responders than men to neuroleptic medication (Hogarty et al. 1974; Seeman 1983). Along related lines, it has been argued that women are more likely than men to be diagnosed as schizophrenic using DSM-II criteria, and rediagnosed as affective disorders using DSM-III criteria (Lewine et al. 1984).

These possible variations in gender-related clinical expression present a particularly complicated problem for ERP investigations because brain electrical activity is influenced by fluctuations in clinical state (Shagass 1972). The fact that schizophrenic females present with less severe symptoms or that schizophrenic males are severely symptomatic for longer periods of time could seriously confound ERP findings. For example, recent studies have reported that late ERP component amplitude may be inversely correlated with the degree of psychopathology (Roth et al. 1980; Josiassen et al. 1981); the implication here is that less symptomatic females would have larger amplitude values than more severely impaired males. ERPs also may be differentially correlated with positive and negative symptoms in schizophrenia (Galdersi et al. 1988; Schwarzkopf et al., in press). The influence of affective symptoms on ERPs in schizophrenia is seen in the recent study of Josiassen et al. (1988) where 20 patients, all diagnosed as having schizophrenia by three diagnostic systems, were rediagnosed as having schizophrenia by DSM-II criteria, and reclassified as affective disorders using DSM-III criteria (Lewine et al. 1984).

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This raises important questions about the gender-related findings in the present study. Are the observed gender effects and gender-related interactions the result of a confounding of clinical state and gender in this study? As summarized in table 2, there was little evidence of obvious clinical difference between the male (n = 34) and female (n = 38) schizophrenic samples. First, there was no statistical evidence of difference in level of functional intelligence; this subject variable has been shown to be an important factor in ERP studies of healthy controls and psychopathological groups (Shagass et al. 1981; Haier et al. 1983; Josiassen et al. 1989). Second, the male and female schizophrenic patients in this sample did not differ in duration of illness, number of hospitalizations, or number of days free from medication. Third, when the combined BPRS scores were statistically compared, there was no overall group difference, and only three univariate t-test comparisons of individual BPRS scales were statistically different. The individual BPRS scales yielding group mean differences were Somatic Concern (females > males), Emotional Withdrawal (females < males), and Conceptual Disorganization (males > females). It is reassuring to note that the level of symptom severity for these three BPRS scales fell in a range that would be considered "mild" or "very mild." Although these data are limited in detail, and do not tap many important domains of relevant observation, the overall findings leave the impression that these samples of male and female schizophrenic patients did not dramatically differ in clinical state at the time of ERP testing.

If the general model of differential clinical expression is unsatisfactory as an explanation of the present findings, then the question of differential histories of drug treatment may be important. Although all patients in this sample had been without psychoactive medication for a median of 10 days, and there was no group difference in the number of days drug free, the effects of centrally active compounds may persist for 6 months or more. Unfortunately, information about the dosages and classes of prior drug therapies of these patients was unavailable or incomplete. It was possible, however, to look at this issue with a second group of 77 medicated schizophrenic patients who took part in ERP testing concurrently with the unmedicated patients in this report. If the neuroleptics being used with this medicated group were divided into piperazine derivatives and non-piperazine derivatives, there was a
highly significant bias toward non-piperazine derivatives being used more frequently with males than females. Thus, the possibility of a systematic gender bias in prescribing practices may be relevant in our understanding of the present ERP differences in male and female patients.

What implications do these exploratory findings of gender effects hold for our understanding of ERP abnormalities observed in schizophrenia? One very clear implication is methodological in nature. Gender-related ERP influences are a crucial source of error variance that bias statistical results even in groups that are carefully matched and balanced for gender. In the presence of such statistical findings, questions about the meaning of gender-related findings are inevitable—particularly about the Diagnosis × Gender interactions which suggest that the presence of schizophrenic illness differentially modifies normal gender influences on ERP characteristics. Could these results be fully explained as some secondary consequence of gender differences in clinical expression of schizophrenia? As demonstrated abundantly in the literature, male and female schizophrenic patients often differ in age of onset, symptom patterns, course of illness, and response to pharmacological treatment. Any of these factors could alter ERP characteristics. The descriptive information in this report, although limited to BPRS and IQ scores, does not leave an impression of obvious clinical differences between the male and female schizophrenic patients in this sample. However, a considerably greater level of detail about symptoms and severity is required to rule out this possibility. In addition, although the duration of illness in these male and female subjects was comparable, the actual age at onset of illness may have needed to be examined. Age at onset may play a more crucial role in the alteration of ERPs than duration of illness.

Another approach toward understanding these Diagnosis × Gender interactions could begin with the neurodevelopmental concept that etiological factors necessary for schizophrenic illness occur very early in brain maturation (Weinberger 1987), resulting in alterations of brain architecture. In light of our growing understanding of sex hormones as determinants of neuronal architecture in the course of prenatal and postnatal brain development, it could be speculated that the putative maturational pathology in schizophrenia disturbs the hormonal processes governing sexual dimorphism. Geschwind and Galaburda (1985a, 1985b, 1985c) have presented a set of hypotheses about prenatal and postnatal hormonal influences on neuronal migration or assembly in the development of sexually dimorphic regions in the human brain. In particular, they speculate on the possible role of testosterone or related factors as a determinant of abnormal formation of sexually dimorphic nuclei in the hypothalamus and in the upper portion of the left temporal lobe, as well as other asymmetries in the human brain. The authors suggest that these architectural abnormalities are implicated in such conditions as developmental learning disorders, immune disorders, and various psychiatric disorders. Obviously, the tools available for such neurodevelopmental investigation are still in a state of infancy and for the near future will be limited to animal studies. However, such a neurodevelopmental framework could integrate the gender-related abnormalities now being studied in regions of the brain in adult schizophrenia (DeLisi et al. 1989), with the well-documented gender differences in clinical expression of schizophrenia, age of onset, course of illness, and response to pharmacological treatment.

Are gender differences in schizophrenia reflected in ERPs recorded from the human brain? One is not easily reassured about the problems surrounding any interpretation of these findings. However, if these observations and speculations about differential ERP gender effects have any merit beyond the obvious statistical implications and are more than secondary consequences of the course and treatment of this illness, then the current effort toward more detailed understanding of gender correlates in schizophrenia may yield valuable clues to the etiology and pathogenesis of this illness.

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