Sex differences in memory processing in schizophrenia: An event-related potential (ERP) study

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Abstract

Recently, research has begun to examine sex differences in cognitive functions in schizophrenia and whether such sex differences reflect normal, exaggerated, or reversed sexual dimorphism. This study examined this question by using event-related potentials (ERPs). ERPs were recorded in a recognition memory task in 18 patients and 18 matched control subjects. On an early frontal component, the results show an interaction between sex and pathological condition that results in an apparent reversed sexual dimorphism. On mid-latency components, patients show no sex difference on a frontal component, but a difference on the posterior component, whereas healthy subjects show a reverse pattern. Finally, late components show sex difference in the same direction as healthy subjects. These results indicate that the influence of sex on the cognitive impairment in schizophrenia is not homogenous across the information-processing cascade.

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1. Introduction

In healthy people, it is well established that women perform better on tasks involving production, comprehension, fine motor skills and perceptual speed; whereas, men perform better on tasks involving visuospatial operations and fluid reasoning (Beatty, 1984; Halpern, 1997; Levy and Heller, 1992). Consistently, women also perform better on episodic memory tasks including delayed recall and recognition than do men, but women and men do not differ on working, immediate and semantic memory tasks (Halpern, 2000; Herlitz et al., 1997, 1999; Silverman et al., 1992; Wilson and Vandenberg, 1978). It has been proposed that the gender differences in memory performance reflect underlying differences in the strategies used to process information (McGivern et al., 1997; Meyers-Levy, 1989). Women processing entails more detailed elaboration of information, whereas men’s processing is more driven by schemas or overall information theme (Meyers-Levy and Maheswaran, 1991; Meyers-Levy and Tybout, 1989).

Similar to the reports in the general population, some studies in schizophrenia have shown women patients perform better than men on tests of attention, verbal memory, and executive function, but worse on tests of spatial memory and visual processing (Goldstein et al., 1998; Seidman et al., 1997). However, other authors reported a reverse pattern (Lewine et al., 1996; Hof et al., 1998), but some of the differences are eliminated when controlling for sex difference in symptom severity. Thus sex may interact with schizophrenia symptoms to affect cognitive functions, especially memory (Gruzelier et al., 1999). Several studies also found no difference in cognitive function between men and women with schizophrenia (Andia et al., 1995; Albus et al., 1997; Goldberg et al., 1995). Again, some of these reports were confounded by differences in symptomatology, age at onset, and medication status. All of these factors must thus be taken into careful consideration when evaluating potential sex differences.

Consistent with the direction of normal sexual dimorphism, morphometric studies in schizophrenia have demonstrated that men have larger ventricles (Andreasen et al., 1990) and smaller frontal and temporal lobe volumes (Andreasen et al., 1994; Bryant et al., 1999; Gur et al., 2000; Reite et al., 1997) relative to women, though not all the studies have found this effect (Flaum et al., 1995; Lauriello et al., 1997). Other studies have reported a significant reduction in anterior cingulate volume in women with schizophrenia relative to healthy women, but no difference between men with and without the diagnosis (Goldstein et al., 2002; Takahashi et al., 2003). This effect is particularly interesting in the light of reports that in the general population women have greater anterior cingulate grey matter volume than men (Paus et al., 1996). Similarly, while in healthy subjects the orbitofrontal cortex to amygdala ratio is higher in women than in men, men with schizophrenia have higher ratio than healthy men and women with schizophrenia have lower ratio than healthy women (Gur et al., 2002). These findings led Gur et al. (2004)
to suggest that schizophrenia involves a reversal of normal sexual dimorphism, i.e., a ‘feminization’ of men and a ‘masculinization’ of women.

Functional magnetic resonance imaging (fMRI) have also shown different patterns of cerebral activations between the sexes during performance in healthy people, though the results have been variable (Halari et al., 2006a,b; Jordan et al., 2002; Lee et al., 2002; Thomsen et al., 2000). A meta-analysis of the functional neuroimaging studies of emotion processing concluded that while women display greater activations than men in the medial limbic structures, men tend to exhibit more activation in the posterior cortices (Wager et al., 2003). There is only a few fMRI evidence of cognitive sex differences in schizophrenia. Our preliminary studies (Mendrek et al., 2005, 2006) showed that men with schizophrenia exhibited overall more widespread and more intense activations than women patients in the same areas where healthy women exhibit normally greater activations than men. Although not coming from a direct comparison between healthy and schizophrenia samples, these observations may represent another example of the possible reversal of normal sexual dimorphism in schizophrenia (but see Halari et al., 2006a,b).

Another method of investigating the functional correlates of cognitive functions is the use of event-related potentials (ERPs). The numerous studies that used this method to differentiate schizophrenia from healthy people have described lower ERP (P300) amplitudes in patients (Ford et al., 1999; Friedman and Squire-Wheeler, 1994; Roth and Cannon, 1972). Nevertheless, this has been found inconsistently, partly depending on symptom severity (Eikmeier et al., 1992; Shenton et al., 1989) and phase of the illness (Mathalon et al., 2000; Pfefferbaum et al., 1989; Strik et al., 1993; Ward et al., 1991). Some studies also reported sex differences in healthy subjects in similar protocol. Generally, women display larger ERP amplitude than men (Desrocher et al., 1995; Hoffman and Polich, 1999; Polich and Martin, 1992). Again the result have been inconsistent, likely depending on the site where ERPs were quantified. In fact, the scalp distribution of ERPs differs in men and women (Golgeli et al., 1999; Hantz et al., 1996), which is consistent with sex difference in processing strategies hypothesized above (Meyers-Levy, 1989; McGivern et al., 1997). However, for the most part, these studies used simple discrimination tasks and limited number of recording sites, thus being unlikely to capture adequately the strategic processes thought to differentiate between sexes. Given the relative consistency of the gender difference in episodic memory, ERP task featuring memory could be more appropriate.

In memory tasks the basic finding is that ERPs elicited, within 250 ms until 800 or 1000 ms post-stimulus, by the first presentation of an item (new item) are less positive than those elicited by the second presentation of the same item (old stimuli) (Rugg and Doyle, 1994). This modulation, referred to as the ‘ERP old/new effect’, is elicited for various types of stimuli (words, pictures or faces) and in a wide variety of tasks (explicit or implicit tasks). In fact, it is composed of a series of ‘effects’ distinct by their task correlates, timing and scalp topography, each reflecting the contribution of a discrete cognitive process, e.g., stimulus categorization, context retrieval, mnemonic binding, to memory performance (Friedman and Johnson, 2000). Some studies using such tasks consistently found abnormalities of the ERP old/new effect in schizophrenia (Guillem et al., 2001b; Kayser et al., 1999; Matsumoto et al., 2001; Matsuoka et al., 1999). A few studies have also used ERP recorded during memory tasks to investigate sex difference in healthy subjects (Everhart et al., 2001; Guillem and Mograss, 2005; Taylor et al., 1990). These studies showed that ERPs from men and women differ in their scalp distribution, particularly on effects related to interference inhibition (early fronto-polar P400) and context processing (later frontal effect overlapping N400 and P600) and in a way that is consistent with a detailed processing in women vs. schema driven processing in men.

This study was intended to assess whether the sex-related difference in schizophrenia patients reflects normal, exaggerated, or reversed sexual dimorphism in memory processing compared to healthy subjects. To this aim, ERPs were recorded in the same recognition memory task that differentiates patients from healthy subjects and men from women in a healthy sample. In order to avoid the reported confounding effects of variables such as symptomatology, age at onset and medication status (Hoff et al., 1998), men and women with schizophrenia were also carefully matched on clinical variables in addition to the usual criteria for matching patient and control groups (e.g., age, sex and socio-educational level).

Our previous findings showed that sex-related ERP differences in healthy subjects encompasses an early fronto-polar component (P400) and a later frontal effect in the N400–P600 time range, both being larger in women than in men. Following the proposal by Gur et al. (2004) and Mendrek et al. (2006; 2006) of a reversal of normal sexual dimorphism, in this study, men with schizophrenia were expected to show larger early fronto-polar component and a later frontal effect than in women with schizophrenia.

2. Method
2.1. Subjects

Eighteen patients (9 men; 9 women) and 18 control subjects (9 men; 9 women) participated in the study. Table 1 presents the socio-demographic and clinical characteristics of the two groups. All the patients met the DSM-IV (SCID-P) criteria for schizophrenia, were in the stable phase of the illness and were receiving outpatient treatment in the urban community of Montreal. They were rated for psychopathology using the Brief Psychiatric Rating Scale (BPRS), the Scale for Assessment of Positive Symptoms (SAPS) and Negative Symptoms (SANS) (Andreasen, 1984a,b). The patients were receiving stable dose of antipsychotic medication for at least two month. The

Table 1

<table>
<thead>
<tr>
<th>Subject’s characteristics (S.D. in parentheses)</th>
<th>Patients</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men (N=9)</td>
<td>Women (N=9)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>35.0 (4.7)</td>
<td>39.6 (7.6)</td>
</tr>
<tr>
<td>Education (years)</td>
<td>13.8 (2.3)</td>
<td>12.6 (3.2)</td>
</tr>
<tr>
<td>SES</td>
<td>3.6 (1.1)</td>
<td>3.4 (0.7)</td>
</tr>
<tr>
<td>Clinical features</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of the illness (years)</td>
<td>10.3 (5.1)</td>
<td>9.7 (6.1)</td>
</tr>
<tr>
<td>Age at onset</td>
<td>24.7 (6.4)</td>
<td>30.0 (8.1)</td>
</tr>
<tr>
<td>BPRS total score</td>
<td>18.0 (7.1)</td>
<td>20.7 (6.1)</td>
</tr>
<tr>
<td>SAPS total score</td>
<td>23.0 (12.8)</td>
<td>19.6 (11.1)</td>
</tr>
<tr>
<td>Hallucination</td>
<td>0.8 (1.2)</td>
<td>0.7 (1.3)</td>
</tr>
<tr>
<td>Delusion</td>
<td>1.8 (1.1)</td>
<td>1.8 (1.5)</td>
</tr>
<tr>
<td>Bizarre behavior</td>
<td>0.7 (1.0)</td>
<td>0.4 (0.9)</td>
</tr>
<tr>
<td>Formal thought disorder</td>
<td>1.1 (1.5)</td>
<td>0.2 (0.7)</td>
</tr>
<tr>
<td>SANS total score</td>
<td>29.2 (20.1)</td>
<td>30.0 (12.4)</td>
</tr>
<tr>
<td>Affective flattening</td>
<td>1.6 (1.2)</td>
<td>1.7 (1.0)</td>
</tr>
<tr>
<td>Alogia</td>
<td>0.4 (0.9)</td>
<td>0.3 (0.7)</td>
</tr>
<tr>
<td>Avolition/apathy</td>
<td>1.7 (1.0)</td>
<td>1.4 (1.2)</td>
</tr>
<tr>
<td>Anhedonia/asociability</td>
<td>1.1 (0.9)</td>
<td>1.4 (1.1)</td>
</tr>
<tr>
<td>Attention</td>
<td>10.9 (8.9)</td>
<td>2.5 (0.5)</td>
</tr>
<tr>
<td>Medication status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antipsychotic</td>
<td>2.9 (1.1)</td>
<td>3.3 (2.9)</td>
</tr>
<tr>
<td>(Eq100 mg CPZ/day)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antioxidants</td>
<td>4.5</td>
<td></td>
</tr>
<tr>
<td>Anticholinergics</td>
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<tr>
<td>Anticonvulsivants</td>
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<td></td>
</tr>
<tr>
<td>Thymeregulators (Li)</td>
<td>0.1</td>
<td></td>
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</tbody>
</table>
mean daily doses for each group in chlorpromazine (CPZ) equivalent are indicated in Table 1.

The control subjects (CTL) were matched on average to the patients for age, and parental socio-educational status (SES). The occupation of the head of household (usually the father) was used as a measure of parental status, and assessed according to the National Occupational Classification (NOC, 1993). In this classification, occupations are assigned to five categories on the basis of the skill level: I = Management, II = Professional occupations, III = Technical, paraprofessional and skilled occupations, IV = Intermediate occupations, V = Laboring and elemental occupations. In this study, the classification was further collapsed such that group 1 corresponds to I or II, group 2 corresponds to III and group 3 corresponds to IV or V of the NOC.

General exclusion criteria for both patients and controls included age less than 18 or greater than 59 years, past or present neurological disorder, non-compliance with testing procedures, abnormal uncorrected vision and, for controls only a history of psychiatric illness, alcoholism or drug abuse. The L-H Lafontaine Hospital research and ethic board had approved the protocol and written informed consent was obtained from participants after thorough description of the study.

2.2. Experimental tasks and stimulus presentation

Stimuli were color front views of unfamiliar faces taken from the MED bank of faces (Debruille et al., 1997) distributed across three blocks. Each block was constructed as a continuous task sequence in which 73 faces occurred the first time (new) and reappeared subsequently once (old) after two to 20 intervening items.

During the test session, subjects were seated in front of a computer monitor placed 1.5 m away. Faces were presented for 500 ms with an ISI varying randomly between 2.5 and 3.5 s (3.0±0.4). Subjects had to indicate, as fast and accurately as possible, whether the current stimulus had been previously presented or not by pressing keys on a computer keyboard. A practice session using faces not included in the test blocks was performed prior to the test in order to familiarize the subject with the task. The order of the three blocks was counter-balanced across subjects and subjects rested for 5 min between each block.

EEG was recorded from 13 scalp sites according to the 10–20 system (Fz, Cz, Pz, Fp1, Fp2, F7, F8, P3, P4, T3, T4, T5 and T6) referenced to linked earlobes. Vertical and horizontal eye movements and blinks (EOG) were monitored via electrodes placed below and on the outer canthus of the eyes. Impedance of all electrodes was maintained below 5 kΩ. Continuous EEG (0.01–30 Hz bandpass) was digitized online (256 Hz) and averaged off-line after EOG correction using statistical software algorithms and rejection of epoch with amplifier blocking. ERPs were computed from 0 to 1000 ms post-onset with a 200 ms pre-stimulus baseline for new and old items. Only ERPs associated with correct responses were analyzed.

2.3. Data analysis

2.3.1. Clinical data

Potential differences between men (M) and women (W) subjects from the two groups on epidemiological variables were assessed using ANOVAs with group and sex as between-subjects factors. Potential differences between male and female patients on the clinical variables were assessed using univariate ANOVAs.

2.3.2. Behavioral data

Reaction times (RTs) were compared using ANOVAs with ‘Group’ (PTS×CTL) and ‘Sex’ (M×W) as between-subjects factors and ‘condition’ (old×new) as within-subject variable. Scores (% correct responses, % false alarms) and the d’-like indices (d′) were calculated and analyzed using ANOVAs with group and sex as between-subjects factors. The d′ is a signal detection index with a logistic distribution that can be interpreted similarly to the d′ index with a normal distribution, but that allows the observation of bias differences among subjects even when performance approaches chance levels (Snodgrass and Corwin, 1988; Kayser et al., 1999).

2.3.3. ERP data

ERPs peaks were identified by visual inspection of the individual traces recorded at Cz within the 200–800 ms post-onset. This epoch was selected as typical for previous studies of the ERP old/new effect. Amplitudes were quantified as the mean amplitude with respect to the 200 ms pre-stimulus baseline within consecutive time windows. For each peak, the lower limit of the time window was defined as the median latency between the current and the previous peak. The upper limit corresponded to the median latency between the current and the following peak. This procedure resulted in non-overlapping time window of varying duration that allows to capture amplitude effects separately for each peak (Guillem et al., 2001a,b).

The data were analyzed separately for midline and lateral sites using mixed-model ANOVAs. For the midline sites, the model included the ‘Group’ (PTS×CTL) and ‘Sex’ (M×W) as a between-subjects factors and the ‘condition’ (old×new) and electrode ‘site’ (Fz, Cz, Pz) as within-subject variables. For the lateral sites, the model included the ‘Group’ (PTS×CTL) and ‘Sex’ (M×W) as a between-subjects factor and the ‘Condition’ (old×new), the ‘Region’ (fronto-polar: Fp1, Fp2; fronto-lateral: F7, F8; anterior temporal: T3, T4; posterior temporal: T5, T6; parietal: P3, P4) and ‘Laterality’ (left, right) as within-subject variables. In all analyses, degrees of freedom were adjusted using the Huynh–Feldt procedure where appropriate (uncorrected df are reported with the epsilon, ε values and corrected p values). Significant interactions involving the factor of group or sex were followed up using planned partial analyses based on waveform examination. Differences in scalp distribution across conditions were also analyzed after normalisation of the data (McCarthy and Wood, 1985), and any effects and interaction involving the factor of site and laterality were reported only if significant on the scaled data set (Swick and Knight, 1997).

3. Results

3.1. Socio-demographic and clinical data

The analysis of the SES data did not show significant effect of group and sex or interaction between the two factors. As usually observed, patients had significantly lower educational levels than controls (F(1,32)=2.12; p =.001), but there was no significant difference between men and women and no interaction between the factors of Group and Sex. Women were slightly but significantly older than men (F(1,32)=5.26; p =.03), but there was no difference between the two groups and no interaction between the factors of Group and Sex. This observation results from the matching of the patients and control subjects and in fact reflects the normal sex distribution of the illness according to age (D’Amato and Rochet, 1995). This is mostly related to the later onset of the illness in women than in men that is also somewhat, although not significantly, present in this study (Table 1). There were no significant differences between men and women on the other clinical variables.

3.2. Behavioral performances

Scores indicate that both patients and controls were above chance in distinguishing new from old stimuli (Table 2). In addition, the absence of significant difference between groups on the sensitivity index (d′) indicates that patients distinguished old from new items as well as controls. Therefore, unspecific effect such as fatigue cannot account for any differences found between groups. At least, if such effect is present, it is likely to affect patients and controls to the same extent.
ANOVA on the global scores (% correctly classified old items) revealed that patients performed significantly lower than controls ($F(1,32)=12.7; p=.001$), but there was no difference between the two groups ($F(1,32)=2.14; p=.15$) and no interaction between the factors of Group and Sex ($F(1,32)=0.07; p=.79$).

ANOVA on RT data showed an interaction between Group and Condition ($F(1,32)=4.84; p=.03$) reflecting that patients benefited less than controls from the facilitation related to items’ repetition (i.e., the behavioral repetition effect). There was no significant effects or interaction involving the factor of Sex (Sex: $F(1,32)=0.08; p=.78$; Group×Sex: $F(1,32)=0.01; p=.92$; Condition×Sex: $F(1,32)=1.47; p=.23$; Group×Condition×Sex: $F(1,32)=0.61; p=.44$).

### 3.3. ERPs

The grand average waveforms presented in Fig. 1 show four peaks similar to those previously reported in the same task in healthy and schizophrenia subjects with slightly different latencies between the patient and control groups (Guillem et al., 2001b, 2003, 2005). These peaks comprise a N300 (PTS: 155–301 ms, CTL: 203–321 ms), a P400 (PTS: 301–418 ms, CTL: 321–421 ms), a N400 (PTS: 418–551 ms, CTL: 421–579 ms) and a P600 (PTS: 551–729 ms, CTL: 579–812 ms).

<table>
<thead>
<tr>
<th>Reaction time (ms)</th>
<th>Patients</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>New</td>
<td>1129.9 (529.8)</td>
<td>1055.3 (230.0)</td>
</tr>
<tr>
<td>Old</td>
<td>1095.3 (336.7)</td>
<td>1134.7 (186.1)</td>
</tr>
<tr>
<td>New–old</td>
<td>34.5 (230.7)</td>
<td>79.4 (119.3)</td>
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</tbody>
</table>

**Scores**

<table>
<thead>
<tr>
<th>% correct</th>
<th>Controls</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>73.1 (20.2)</td>
<td>64.8 (18.2)</td>
</tr>
<tr>
<td>Women</td>
<td>73.9 (7.9)</td>
<td>5.1 (5.6)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>% false alarms</th>
<th>Controls</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>12.3 (2.3)</td>
<td>5.1 (5.6)</td>
</tr>
<tr>
<td>Women</td>
<td>13.7 (10.8)</td>
<td>9.5 (5.1)</td>
</tr>
</tbody>
</table>

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<thead>
<tr>
<th>$d_L$</th>
<th>Controls</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>3.5 (1.8)</td>
<td>4.0 (1.5)</td>
</tr>
<tr>
<td>Women</td>
<td>4.0 (1.5)</td>
<td>3.8 (1.9)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Behavioral results (S.D. in parentheses)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients</td>
</tr>
<tr>
<td>Reaction time (ms)</td>
<td></td>
</tr>
<tr>
<td>New</td>
<td>1129.9 (529.8)</td>
</tr>
<tr>
<td>Old</td>
<td>1095.3 (336.7)</td>
</tr>
<tr>
<td>New–old</td>
<td>34.5 (230.7)</td>
</tr>
</tbody>
</table>

**Fig. 1.** Representative grand average waveforms recorded in men and women with and without schizophrenia.
Moreover, there was a trend for an interaction between Group and Sex (F(1,32)=2.17; p<.05) and Site×Group×Sex (F(4,128)=2.65; p=.05). More importantly, there was an interaction between Group and Sex (F(1,32)=10.94; p<.005; \(\varepsilon=.842\)).

The ANOVA on lateral data revealed significant effects of Condition (F(1,32)=15.80; p<.0005; \(\varepsilon=.481\)) and Laterality (F(1,32)=10.62; p<.0005). There was also a significant Condition×Site×Sex (F(4,128)=3.92; p<.05), Group×Site×Laterality×Sex (F(4,128)=3.42; p<.05), and Condition×Site×Laterality×Sex (F(4,128)=3.42; p<.05) interactions indicating sex differences in the topographical distribution of the ERP old/new effect. Moreover, there was a significant Group×Sex (F(1,32)=4.50; p<.05) and Site×Group×Sex (F(4,128)=4.57; p<.05) interaction indicating the sex differences in ERP topography are different in healthy subjects and patients.

Examination of Fig. 2A (old/new difference collapsed across groups) shows that the interaction involving the factors of Condition, Site and Sex reflects larger old/new effect in women than in men at frontal sites (over the right hemisphere in healthy subjects and bilaterally in patients). This was confirmed by the Condition×Site×Laterality×Sex interaction that was significant on partial analyses over frontal sites (Fp1, Fp2, F7, F8) (F(1,32)=5.66; p<.05). Although Fig. 2A suggests that this sex difference is also present over posterior sites, the partial analysis (P3, P4, T5, T6) showed no significant effects involving the factor of Sex.

Examination of Fig. 2B (amplitudes collapsed across conditions) reveals that the interactions involving both factors of Group and Sex reflect a reversal of sex difference in patients compared to control subjects. In patients, the ERPs are more positive in men than in women particularly over frontal and temporal sites bilaterally. The reverse is observed in controls; i.e. women more positive than men about the same scalp distribution. Partial analyses confirmed the significant Group×Sex interaction over fronto-temporal sites (Fp1, Fp2, F7, F8, T3, T4) (F(1,32)=8.00; p<.008), which is absent over posterior sites (P3, P4).

These results indicate the presence of two distinct components previously described in this time window at the same locations (Guillem et al., 2003, 2005). The first has been assimilated to the P2a, a bilaterally distributed fronto-polar component. This component shows an inversion of sex difference in patients compared to controls. The second component that corresponds to the classical posterior N2b shows no sex-related difference (Fig. 1).

### 3.3.2. P400 time window

The ANOVA on midline data for the P400 resulted in significant effects of Condition (F(1,32)=9.32; p<.005) and Site (F(2,64)=3.81; p<.05). There was also a significant Group×Condition×Site×Laterality×Sex interaction (F(4,128)=6.69; p<.005) indicating sex differences in the lateral distribution of the ERP old/new effect. Examination of Fig. 3A (old/new difference collapsed across groups) shows that this interaction reflects a lower old/new effect in women than in men over left fronto-temporal sites. This was confirmed on a partial analysis (F7, F8, T3, T4) showing a largely significant Condition×Site×Sex interaction (F(1,32)=4.16; p<.05) indicating sex differences in the lateral distribution of the ERP old/new effect. Examination of Fig. 3B (amplitudes collapsed across conditions) shows that this interaction reflects a double-sided effect. First, there is a sex difference in amplitude (men > women) bilaterally over fronto-
temporal sites in controls that is not present in patients. This was confirmed by the significant Group×Sex interaction \((F(1,32)=5.70; p=.02)\) on partial analyses (Fp1, Fp2, F7, F8, 3, T4). Second there is a sex difference in amplitude (men>women) over left temporo-parietal sites in patients that is not present in controls. Partial analyses (P3, P4, T5, T6) showed a main effect of Group \((F(1,32)=5.74; p=.02)\) indicating generally lower amplitude in patients than in controls. There was also a significant Laterality×Sex interaction \((F(1,32)=3.98; p=.05)\) and a trend for a Site×Group×Sex interaction \((F(1,32)=2.98; p=.09)\). Altogether, these results indicate that the sex difference in this time window involves three distinct components. First, a bilateral and central frontal component shows a difference in amplitude between men and women in controls, but not in patients. It seems to correspond to the frontal component for which sex differences have been reported in other studies (Guillem et al., 2005). Second, a left posterior component shows a difference in amplitude between men and women with schizophrenia, but not in patients. It corresponds to the well-documented parietal N400. In this time window, there is thus no actual reversal of the sex difference between patients and controls, as reported in the earlier time window, but rather a variation in the topography of the sex difference, i.e., frontal in controls vs. left posterior in patients. This observation indicates that sex differences involve distinct processes in the two groups. The third is a left fronto-temporal component that is modulated, i.e., shows an ERP old/new effect, in men, not in women, but similarly in patients and controls (see below and Fig. 4). It will be subsequently referred to as the late fronto-temporal effect (LFT).

3.3.4. P600 time window

ANOVA on the midline data obtained in the P600 time window showed significant effects of Condition \((F(1,32)=5.18; p=.03)\) and Site \((F(2,64)=5.26; p=.01; \epsilon=.765)\), and Group \((F(1,32)=7.87; p=.008)\), but no effect involving the factor Sex reached the significance level.

The ANOVA on lateral data revealed significant effects of Condition \((F(1,32)=4.55; p=.04)\), Site \((F(4,128)=21.28; p<.0005; \epsilon=.518)\), Laterality \((F(1,32)=4.24; p=.05)\) and a significant Site×Laterality interaction \((F(4,128)=6.34; p=.001; \epsilon=.680)\). There was also a significant Condition×Laterality×Sex interaction \((F(1,32)=7.24; p=.01)\) indicating differences in the laterality of the ERP old/new effect between men and women. Fig. 4A shows that these results reflect generally larger ERP old/new effect (central and right sites) in women compared to men except for left fronto-temporal sites (F7, T3) over which the old/new effect is present in men but not in women. The direction and topography of this difference suggest that it is the continuation of the frontal effect described in the N400 time window.

Finally, there was a significant main effect of Group \((F(1,32)=5.77; p=.02)\), and a significant Condition×Site×Group interaction \((F(4,128)=5.09; p=.01; \epsilon=.407)\) indicating that patient and control groups differ in the topography of the ERP old/new effect. Fig. 4B shows that these

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**Fig. 3.** Scalp distribution of the ERP old/new effect (old−new difference) averaged across groups (A) and of the ERP mean amplitudes obtained in the two patient groups (B), within the N400 time window.

**Fig. 4.** Scalp distribution of the ERP old/new effect (old−new difference) averaged across groups (A) and across sex (B), within the P600 time window.
results involve two distinct effects. First, there is a reduction of ERP old/new effect over temporo-posterior sites, mostly over the right hemisphere (T3, T6, P4) in patients. Owing to its topography and latency, this effect is likely to reflect group differences in the modulation of the well-described P600 component of the ERP old/new effect. Second, the ERP old/new effect is enhanced over frontal and central sites (Fz, Fp1, Fp2, F7, F8) in patients compared to controls. This has been already described as a delayed and enhanced bilateral frontal effect in schizophrenia patients (Guillem et al., 2001a,b, 2003). It is noteworthy that there was no interaction between, or involving, both the factors of Group and Sex. Therefore, the reduced P600 old/new effect in patients is unrelated to the lower effect in men, and similarly, the enhanced frontal old/new effect in patients is unrelated to the larger amplitude found in women.

4. Discussion

4.1. Behavioral performances

As in previous studies using the same task and stimuli (Guillem et al., 2001a,b, 2003), patients performed significantly lower and showed less repetition facilitation than controls. This result is consistent with the numerous reports of the memory impairment in tasks requiring the conscious recollection of information such as unfamiliar faces (Huron et al., 1995; Whitmeyer et al., 2001).

The results also show that men of both groups, committed significantly more false alarms than women. The similar trend observed in a previous study on healthy subjects (Guillem and Mograss, 2005) has been interpreted as reflecting the fact that men form less specific representations, i.e., are more sensitive to subjective familiarity (Schacter et al., 1998) and interference (Kramer et al., 1997; Palmer and Folds-Bennett, 1998) than women. This interpretation would also agree with the view that sex differences in memory rely on strategic difference, women entailing more detailed elaboration of information, and men processing being mainly driven by schemas or overall information theme (Myers-Levy and Maheswaran, 1991; Meyers-Levy and Tybout, 1989). Further, the absence of any interaction between Group and Sex indicates that, although patients perform at a lower level, the strategic mechanisms respectively involved in men and women are not different in schizophrenia patients and healthy subjects.

4.2. ERPs

4.2.1. Early frontal effect

The first result is that both schizophrenia and healthy women elicit a larger ERP old/new effect over frontal sites (Fig. 2A). A similar trend has been obtained in a previous study although somewhat later in the P400 time window (Guillem and Mograss, 2005). This early frontal old/new effect has been related to the inhibition of information irrelevant to accurately perform the task, i.e., interference (Guillem et al., 2001a,b; Melara et al., 2002; Tsvilis et al., 2001). By this view, the larger effect in women indicates a facilitated processing of old items; i.e., less interference inhibition is required, than in men. As for the behavioral data on false alarms rates, this interpretation agrees with the view that women entail more detailed processing (Meyers-Levy and Maheswaran, 1991; Meyers-Levy and Tybout, 1989).

However, the situation appears more complex when examining the ERP amplitudes averaged across conditions within this time window. In healthy subjects, women exhibit more positive amplitude than men (Fig. 2B). Consistent with the interference inhibition interpretation, it has been proposed that ERP amplitude within this time window involves a P2a that is proportional to stimulus salience (Guillem et al., 2003, 2005; Potts et al., 1998; Potts et al., 2002) (i.e., more positive amplitude reflects more salient information, hence less interference inhibition). Thus, again the results indicate that healthy women rely on more salient and interference resistant representation than men, likely due to their more detailed processing. The reverse is observed in patients, in whom men exhibit larger ERP amplitudes than women (Fig. 2B). This implies that women with schizophrenia form less salient representations than men. Moreover, contrary to the general population, men with schizophrenia entail detailed processing, whereas women’s processing relies mainly on schemas. This interpretation agrees with Gur et al.’s (2004) proposal of a reversed sexual dimorphism in schizophrenia, but contrasts with the above described finding of the ERP old/new effect and false alarm rates, which suggests that women, with or without schizophrenia, are less sensitive to interference. Overall, it has been demonstrated that schizophrenia is characterized by difficulties in using redundancies to diminish processing requirements and to bind and organize information with each other, mostly because they focus on processing details at the expense of the whole picture (Cutting, 1985; Danion et al., 1999; Hemsley, 1987; Magaro, 1984). In fact, the combination of this schizophrenia-related impairment with the normal sex-related difference in processing strategies may well account for the observed reversal. Because of the conjunction of a normal sex and disease-related tendency to focus on details schizophrenia women would need more interference inhibition to achieve correct recognition. Conversely, in men with schizophrenia, the processing of details related to the disease would be somehow counterbalanced by the normal men tendency to schematic processing, hence requiring less interference inhibition.

4.2.2. Bilateral frontal component

Within the N400 time window, the results show a sex difference bilaterally over frontal sites in healthy subjects. ERP amplitude is larger, i.e., more positive in women than in men. The similar sex difference evidenced in our previous study (Guillem and Mograss, 2005) has been attributed to the frontal component often associated with strategic monitoring processes (Allan et al., 1998; Friedman and Johnson, 2000). More specifically, in face processing it could represent the processing of person-specific information (Paller et al., 2000) or of the intrinsic contextual attributes of faces (Guillem et al., 2001a,b). These observations are thus in accordance with the view of a more detailed elaboration in women than in men. In schizophrenia, anomalies in the old/new modulation of this component have been also described (Guillem et al., 2001a,b, 2003). It is larger and lasts longer than in healthy subjects (see also Fig. 4B), particularly in patients with high reality distortion symptoms (delusions and hallucinations). This anomaly has been interpreted as reflecting the inappropriate processing of contextual information associated with reality distortion. The present results show that the sex difference on this component observed in healthy subjects is not present in patients. Consistent with the interpretation of this frontal component, it could be that the general pathological tendency of schizophrenia patients to focus on details has abolished the normal sex difference. This is also supported by the observation that men and women patients do not differ in symptoms, particularly reality distortion, scores (Table 1). Thus, the results indicate that the pathological mechanisms related to the illness are transcending normal sex differences.

4.2.3. Posterior component (N400)

As in the previous study, the results show no sex difference on the posterior N400 in healthy subjects. The consensus about the posterior N400 is that it is modulated by the ease with which the incoming information is integrated with personal knowledge (i.e., the more positive the amplitude, the easier the integration) (Holcomb, 1993; Rugg and Doyle, 1994). Thus, the result indicates that information is integrated to the same extent in women and men. This is reminiscent with the lack of gender difference on semantic memory and priming tasks reported in behavioral studies (Herlitz et al., 1997). It should be
mentioned that another ERP study of memory processing has shown sex difference of the N400 (Taylor et al., 1990). However, as discussed elsewhere (Guillem and Mograss, 2005), this apparent discrepancy is likely related to difference in the nature (verbal vs. faces) of the stimuli.

In contrast to healthy subjects, we have observed a sex difference in patients. Men with schizophrenia showed larger left posterior and central N400 amplitude than women, indicating that they generally elicit more integration effort (for both old and new stimuli). As for the early component, this result could be viewed as arising from the combination of schizophrenia-related impairment with normal sex-related difference in processing strategies. The disease-related processing of details would enforce men to greater integration effort to compensate for their natural tendency to schematic processing.

4.2.4. Late fronto-temporal effect (LFT)

Overlapping the N400 and the later time window, a lower ERP modulation is elicited over left fronto-temporal sites in women compared to men and in controls compared to patients. Frontal components within the 500–2000 ms have been often described in memory task involving source judgment, although mostly over the right hemispheres (Senkfor and Van Petten, 1998; Wilding, 1999; Wilding et al., 1995). In fact, because the same activity is elicited for unsuccessful retrieval and false alarms, it seems more related to post-decisional processes contingent upon retrieval or validation of contextual information rather than source retrieval per se (Friedman and Johnson, 2000; Guillaume and Tiberghien, 2005; Trott et al., 1999). It is unclear whether the present left lateralized component reflects the same processes as the right component. However, this interpretation would be consistent with the behavioral results showing that men committed more false alarms than women, as well as with the well-known tendency (not significant here) of schizophrenia patients to make false alarms too. Interestingly, an effect similar in latency and scalp distribution has recently described in schizophrenia patients has been related to impulsivity (Guillem et al., 2005). Then again, the results are consistent with observations of false alarm rates and with the tendency of men to be more impulsive than women. Although no interaction was found here, the difference between patient and controls may also not be completely independent from sex since women with schizophrenia display more impulsive symptoms than men (Leung and Chue, 2000).

4.2.5. Late positive component (P600)

Over posterior sites, the recordings display the classical P600 old/new effect, which is larger in women than in men for both groups (Fig. 4A). The posterior P600 effect is assumed to reflect the mnemonic binding component that links the different aspects of an information into a coherent, i.e., elaborated representation (Guillem et al., 2001a,b; Van Petten et al., 1991). Thus again, the sex difference on this effect is in accordance with the more detailed elaboration of information in women. However, this difference was not present in our previous study (Guillem and Mograss, 2005). Likely, this discrepancy can be attributed to age difference between the subject samples of the two studies. Studies have indeed shown interaction between age and sex on memory function (Bleecker et al., 1988; Larrabee and Cook, 1993). For instance, in young adults (16–47 years), a memory decline is observed in men but not in women, whereas in older adults (55–89 years) the decline is similar in both sexes (Kramer et al., 2003). In the previous study, healthy subjects were younger on average (men: 27±5.5; women: 24.7±3.6) than here (men: 34.2±6.6; women: 40.6±9.4), and the study, healthy subjects were younger on average (men: 27.6±5.5; women: 24.7±3.6) than here (men: 34.2±6.6; women: 40.6±9.4), and in the present study, the scores were SAPS=21.3±12.7 and SANS=29.6±16.2, i.e., closer to those of the RD group. Noteworthy, this effect of symptom may not be completely independent from age since positive symptoms are known to decrease during the course of the illness. Given the interaction between age and sex, it may also not be completely independent from sex. Although no difference was found here, men with schizophrenia have been shown to have more pronounced negative symptoms than women (Kay et al., 1986; Ring et al., 1991; Schultz et al., 1997).

5. Conclusion

In summary, this study may add some light on the discrepancies found in the literature on cognitive and brain sex differences in schizophrenia. As mentioned, some researcher described sex differences in the same direction as in healthy people, whereas others have found either no sex difference or difference opposite to healthy subjects. In fact, the present results show that the three cases are possible depending on the cognitive processes being considered. Early processes, i.e., interference inhibition, show an interaction between sex and the pathological condition resulting in an apparent reversal of normal sexual dimorphism. On the mid-latency processes, schizophrenia entails a change in the topography and direction of sex difference. Patients show no sex difference on frontal, i.e., context processing indices, whereas healthy subjects show a women-men difference. Conversely, healthy subjects show no sex difference on parietal, i.e., knowledge integration indices, whereas patients show a men-women difference. Finally, the late processes indexed by LPC and LFT display sex difference in the same direction as in healthy subjects. These observations clearly indicate that the influence of sex on the cognitive impairment in schizophrenia is not homogenous. Rather, as previously suggested by Gruzelier et al. (1999), the observed difference in cognitive processing between men and women with schizophrenia appears to result from the interaction between the normal sex difference in processing strategies and pathological processing biases related to the illness.

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