Progress in Neuro-Psychopharmacology & Biological Psychiatry 33 (2009) 1–10

Contents lists available at ScienceDirect

Progress in Neuro-Psychopharmacology & Biological Psychiatry

journal homepage: www.elsevier.com/locate/pnpbp

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

François Guillem *, Adrianna Mendrek, Marc E. Lavoie, Tania Pampoulova, Emmanuel Stip

Centre de Recherche F-Seguin – Hôpital L-H Lafontaine, 7331, Rue Hochelaga, Montreal, Québec, Canada H2L 1L8

ARTICLE INFO

Article history:
Received 23 April 2008
Received in revised form 9 July 2008
Accepted 3 August 2008
Available online 7 August 2008

Keywords:
Event-related potentials
Memory
Schizophrenia
Sex

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.

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 men and women 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 (Myers-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; Hoff 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)

Abbreviations: BPRS, Brief Psychiatric Rating Scale; CPZ, Chlorpromazine; CTL, Control subjects; DSM-IV, Diagnostic Statistical Manuel IVth edition; EEG, Electro-encephalogram; EOG, Electro-oculogram; ERPs, Event-Related Potentials; *f*MRI, Functional Magnetic Resonance Imaging; LFT, Late Fronto-Temporal effect; LPC, Late Positive Component; M, Men; PTS, Patients; RD−, low level of reality distortion; RD+, high level of reality distortion; SANS, Scale for Assessment of Negative Symptoms; SAPS, Scale for Assessment of Positive Symptoms; SCID-P, Structured Clinical Interview for DSM disorders — Psychotic screen; SES, socio-educational status; W, Women.

* Corresponding author. Tel.: +1 514 251 4015; fax: +1 514 251 2617.
E-mail address: francois.guillem@umontreal.ca (F. Guillem).

0278-5846/$ – see front matter © 2008 Elsevier Inc. All rights reserved.
doi:10.1016/j.pnpbp.2008.08.002

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 (*f*MRI) 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 *f*MRI 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 aviations 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
Subject's characteristics (S.D. in parentheses)

	Patients		Controls	
	Men (*N*=9)	Women (*N*=9)	Men (*N*=9)	Women (*N*=9)
Age (years)	35.0 (4.7)	39.6 (7.6)	34.2 (6.6)	40.6 (9.4)
Education (years)	13.8 (2.3)	12.6 (3.2)	18.2 (3.8)	16.4 (4.1)
SES	3.6 (1.1)	3.4 (0.7)	3.0 (1.0)	3.4 (1.1)
Clinical features				
Duration of the illness (years)	10.3 (5.1)	9.7 (6.1)		
Age at onset	24.7 (6.4)	30.0 (10.1)		
BPRS total score	18.0 (7.1)	20.7 (6.1)		
SAPS total score	23.0 (12.8)	19.6 (13.1)		
Hallucination	0.8 (1.2)	0.7 (1.3)		
Delusion	1.8 (1.1)	1.8 (1.5)		
Bizarre behavior	0.7 (1.0)	0.4 (0.9)		
Formal thought disorder	1.1 (1.5)	0.2 (0.7)		
SANS total score	29.2 (20.1)	30.0 (12.4)		
Affective flattening	1.6 (1.2)	1.7 (1.0)		
Alogia	0.4 (0.9)	0.3 (0.7)		
Avolition/apathy	1.7 (1.0)	1.4 (1.2)		
Anhedonia/asociality	1.1 (0.9)	1.4 (1.1)		
Attention	1.0 (0.9)	2.5 (0.5)		
Medication status				
Antipsychotic (Eq100 mg CPZ/day)	2.2 (1.1)	3.3 (2.9)		
Anxiolytics	4	5		
Anticholinergics	1	3		
Anticonvulsivants	2	0		
Thymoregulators (Li)	0	1		