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Disturbed sexual dimorphism of brain activation during mental rotation in schizophrenia

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ABSTRACT

Background: Sex differences in visuo-spatial abilities have been well documented in the general population, but there are only a few inconsistent reports in schizophrenia. The purpose of the present study was to examine potential sex differences in performance and pattern of brain activations during mental rotation in schizophrenia patients relative to control participants.

Methods: Thirty three schizophrenia patients (17 women and 16 men) were compared to thirty five healthy control participants (17 women and 18 men), while performing a classic mental rotation task (3-D figures). Blood oxygen level dependent (BOLD) echo-planar images were acquired on a 3-Tesla Siemens TRIO system. Random-effect analyses were performed using SPM5 (UK Wellcome Institute).

Results: Behavioural data revealed a diagnosis-by-sex interaction with healthy men (HM) performing significantly better than schizophrenia men (SZ-M) and no significant difference between healthy women (HW) and schizophrenia women (SZ-W). fMRI results revealed an overall similar pattern of extensive cerebral activations (in the parietal and lateral prefrontal cortex) and deactivations (in the medial prefrontal cortex) in HM and SZ-W during performance of the mental rotation versus control task. In contrast, both HW and SZ-M showed much more restricted activations and no significant deactivations.

Conclusions: Sex differences in performance and cerebral activations during mental rotation in schizophrenia patients deviated significantly from what we observed in healthy volunteers. This finding supports and extends existing evidence of a disturbed sexual dimorphism in schizophrenia. Moreover, the results emphasize the importance of including both sexes in neurocognitive and neuroimaging studies of schizophrenia.

1. Introduction

Schizophrenia is a severe and complex psychiatric disorder that differs between women and men in terms of age at onset, symptomatology, response to medication, and structural brain abnormalities (Frazier et al., 2008; Goldstein et al., 2002; Grossman et al., 2008; Leung and Chue, 2000). Research investigating sex differences in cognitive function of schizophrenia patients has demonstrated marked variability in their results. For example, while some studies have shown more deficits in men relative to women patients in attention, language, and executive functions (Goldstein et al., 1994; Seidman et al., 1997), others have found the opposite effect (Lewine et al., 1996; Perlick et al., 1992) or no significant differences between the sexes (Andia et al., 1995; Goldberg et al., 1995). The studies of functional neuroanatomy underlying sex differences in cognitive abilities in schizophrenia are lacking altogether.

The main purpose of the present study was to examine sex differences in brain function associated with visuo-spatial abilities in schizophrenia patients relative to healthy control

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participants. We have chosen a mental rotation task because it has been shown to consistently elicit differences between healthy men and women in terms of reaction time and performance accuracy (Gootjes et al., 2008; Halari et al., 2006; Kozaki and Yasukouchi, 2009). In addition, this task has evoked a differential pattern of brain activation between the sexes. In one of the earliest studies, Thomsen et al. (2000) found more activity in the superior parietal lobe in men relative to women. Subsequent studies have often reported greater activations in the parietal cortex (inferior and superior) in males relative to females, while females showed increased activations in the frontal areas (inferior and lateral) (Hugdahl et al., 2006; Weiss et al., 2003c).

To our knowledge there have been no published studies of differences between women and men with schizophrenia during performance of mental rotation, except for our previous report of preliminary behavioural data in a sub-sample of patient and controls that were subsequently included in the present study. Specifically, we have found the expected sex difference in control participants (i.e. men faster and more accurate than women) and an unexpected reversal of normal sexual dimorphism in patients (i.e. women faster and more accurate than men) (Jimenez et al., 2009). Thus, based on existing literature and our preliminary findings, we hypothesized that schizophrenia men will present decreased cerebral activity relative to healthy men in regions previously implicated in mental rotation (superior and inferior parietal cortex, precuneus) and will have a worse performance. On the other hand, we predicted that schizophrenia women will not show the deficit in cerebral activity and performance relative to healthy women, but that both women groups will activate the parietal cortex and the lateral prefrontal cortex.

2. Materials and methods

2.1. Subjects

Thirty three schizophrenia patients (17 women and 16 men) meeting the DSM-IV criteria for schizophrenia (American Psychiatry Association, 1994), in a stable phase of their illness (defined as no relapse within the last two months and no change in their antipsychotic treatment within the last month) and 35 healthy controls (17 women and 18 men) participated in the study. All participants were right-handed (84.93 ± 3.21; Edinburgh Inventory) (Oldfield, 1971). The groups were matched for age and parental socio-economic status (National Occupational Classification; NOC) (Census, 2001), (Table 1).

All patients were re-evaluated by experienced psychiatrists before being assigned to the research group (DSM-IV, criteria A–E); affective, schizoaffective and schizophreniform psychoses were excluded. Control participants were screened with the non-patients edition of Clinical Interview for DSM-IV (SCID) (First et al., 1996).

Symptom severity was rated according to the positive and negative syndrome scale (PANSS) (Kay et al., 1986). Illness onset was defined as the date of the first psychiatric consultation. All patients received at least one atypical antipsychotic (25 patients received one, 7 received two, 1 received three; clozapine: $n = 19$, mean dosage $= 452.63\,\text{mg} \pm 77.23\,\text{mg}$; olanzapine: $n = 11$, mean dosage $= 15\,\text{mg} \pm 5.6\,\text{mg}$; risperidone: $n = 8$ mean dosage $= 4.00 \pm 1.85$ mg; quetiapine: $n = 5$, mean dosage $=$ 550.00 mg $\pm$ 277.82 mg) (chlorpromazine equivalence was calculated) (Woods, 2003), (Table 1).

General exclusion criteria included age below 18 or above 45 years, past or present neurological or Axis-I psychiatric disorder, alcoholism or drug abuse, non compliance with testing procedures, abnormal uncorrected vision or any contra-indication for MRI such as a cardiac pacemaker, an aneurysm clip, a metal prostheses or cardiac valve replacement, the presence of metal in an eye or any part of the body, certain dental work or claustrophobia.

In accordance with the Declaration of Helsinki, written informed consent was obtained prior to participation in the experiment. The ability of schizophrenia patients to give informed consent was established using the guidelines of the Canadian Psychiatric Association (Arboleda-Florez, 1997). The study was approved by the ethics committees of the Fernand-Seguin Research Center of the Louis-H Lafontaine Hospital and the Regroupement Neuroimagerie Québec.

2.2. Procedure

Our version of the mental rotation task consisted of an 8-minute run of alternating 38-second blocks of experimental and control conditions with 20-second periods of rest separating the blocks from one another. Both types of blocks (experimental and control) were repeated four times during the course of the functional run and involved presentations of pairs of black-and-white drawings of 3-D shapes, adopted from Shepard and Metzler's (1971) mental rotation task (Shepard and Metzler, 1971). In the experimental condition, one shape was rotated along its vertical axis relative to the other shape. In half of the trials, the figures were identical to each other, whereas in the other half they were mirror images

Table 1
Demographic and clinical rating data (means and standard deviations).

	Control group		Schizophrenia group		Statistics Independent samples Student
	Men $N = 18$	Women $N = 17$	Men $N = 16$	Women $N = 17$	
Age (years)	31.64 (6.50)	32.38 (7.69)	33.17 (7.72)	32.11 (7.76)	$F(1, 68) = 0.739; p = 0.734$
Parental SES	3.2 (0.9)	3.4 (1.1)	3.5 (1.2)	3.4 (1.3)	$F(1, 68) = 0.486;\ p = 0.346$
Age at onset			23.58 (6.24)	20.27 (4.12)	$t = 1.86;\ p = 0.72$
Duration of illness years			10.66 (7.55)	12.88 (7.82)	$t = 1.30;\ p = 0.20$
Chlorpromazine equivalents, mg			611.39 (294.72)	740.35 (389.34)	$t = 1.79;\ p = 0.08$
PANSS total			83.23 (29.41)	76.33 (9.64)	$t = 0.944;\ p = 0.352$

Subject's characteristics (S.D.in parentheses). On the basis of t tests, there were no statistically significant differences for these characteristics between the sexes within group or between groups within sex. Edinburgh Inventory: All right (84.93 ± 3.21).