Schizophrenia Research 134 (2012) 171–179

Contents lists available at SciVerse ScienceDirect

Schizophrenia Research

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

Decreased activity in right-hemisphere structures involved in social cognition in siblings discordant for schizophrenia

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ARTICLE INFO

Article history:
Received 15 July 2011
Received in revised form 8 November 2011
Accepted 9 November 2011
Available online 3 December 2011

Keywords:
Schizophrenia
Siblings
Social cognition
Theory of mind
fMRI
Lateralization

ABSTRACT

Background: Social cognitive deficits contribute to functional disability in schizophrenia. Social cognitive tasks in healthy persons consistently evoke activation of medial prefrontal cortex, inferior frontal gyrus, temporoparietal gyrus, and posterior cingulate cortex/precuneus. We tested the hypothesis that patients with schizophrenia and their unaffected siblings share dysfunction of the same neural networks.
Methods: Neural activation during emotion processing (EP), theory of mind (ToM), and control tasks was measured using functional magnetic resonance imaging (fMRI) in 14 patients with schizophrenia, 14 nonpsychotic siblings of patients with schizophrenia, and 14 matched healthy subjects.
Results: Compared with healthy controls, patients with schizophrenia showed reduced activation of right hemisphere structures involved in EP and ToM including inferior frontal gyrus, middle frontal gyrus, and right temporoparietal junction. These deficits were shared, in part, by unaffected siblings. The latter group demonstrated deficits in bilateral precuneus activation during ToM, not present in patients.
Conclusions: Schizophrenia appears to be associated with a deficit in activation of right hemisphere components of a ToM network. Such deficits are shared in part by those at high genetic risk but unaffected by schizophrenia.

1. Introduction

Social functioning disturbances have long been recognized as an essential feature of schizophrenia, usually present before the onset of other symptoms, and persisting after the latter have abated (Kraepelin, 1899). The syndrome has a strong heritability, but it is highly unlikely that a single genetic alteration will account for the whole range of clinical manifestations (Weinberger, 2002). This has led to an effort to dissect the many behavioral abnormalities of the disease into discrete pathophysiological mechanisms, with the hope that each will have a simpler heritability than the syndrome as a whole (Weinberger, 2002). This might, in turn, facilitate the search for specific genes involved in the etiology of the disease. Such discrete pathophysiological features, termed endophenotypes or intermediate phenotypes, are quantifiable psychophysiological, neurocognitive, and motor variables, shown to be altered not only in schizophrenia, but also in at-risk subjects — notably, the patients' close relatives, who share with them a significant proportion of genes (Radant et al., 2010; Stone et al., 2011). These are shown to contribute to deficits of social cognition and disability seen in schizophrenia (Sergi et al., 2007). There is a paucity of studies seeking to define social cognitive intermediate phenotypes of social cognition, and to the extent of our knowledge, available studies exploring brain activity during social cognitive tasks in patients and at-risk subjects have involved emotion processing (EP) paradigms only (Habel et al., 2004; Rasetti et al., 2009). This might reflect the fact that brain networks subserving theory of mind (ToM) in normal conditions have only recently been outlined, and its components are still surrounded by controversy (Mar, 2011). Moreover, some data indicate that EP and ToM are closely interrelated phenomena, as judging other persons' intentions in facial expression does involve the evaluation of their emotional status as well as one's own response to it (Ochsner, 2008). This is most evident in tests involving recognition of facial expressions,

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doi:10.1016/j.schres.2011.11.010

which are often used in the measurement of either variable (Ochsner, 2008).

The aim of this study was to determine whether EP and ToM networks in patients with schizophrenia and their unaffected siblings differ from those in healthy controls. We hypothesized that brain activation patterns underlie performance during social cognition tasks (Benedetti et al., 2009), and on the basis of previous results on task performance (Anselmetti et al., 2009; de Achaval et al., 2010) expected brain activation during EP and ToM tasks to be similar in patients and their nonpsychotic siblings. More specifically, we predicted that abnormalities in relatives would include deficits that are less severe than those seen in patients, and perhaps with additional abnormalities as a consequence of untreated deficits (de Achaval et al., 2010).

Tasks involving the face and eyes have traditionally been used to measure abilities of EP and ToM, i.e., the capacity to infer the mental states and intentions of others (Baron-Cohen et al., 1997). In this study, we used the same stimuli in both control and experimental tasks by asking the participant to state the gender or the emotion/mental state respectively (Baron-Cohen et al., 1999a, 1999b; Russell et al., 2000; Habel et al., 2004). Given the nature of the stimuli (human expressions) and responses (choosing the correct word), we expected to observe involvement of mirror neuron systems and mentalizing or ToM systems on functional magnetic resonance imaging (fMRI) scanning (Pelphrey et al., 2004; Amodio and Frith, 2006; Van Overwalle and Baetens, 2009). In addition, stimuli used in the present study would be expected to evoke significant activation of language areas in the left hemisphere in all groups (Baron-Cohen et al., 1997; Lee et al., 2006). However, language aspects probed in our study are less concerned with phonology, syntax, and morphology (i.e., functions typically associated with the dominant hemisphere), and more with motor nonverbal expressions conveying actual meaning (associated with right-hemisphere processing; Mitchell and Crow, 2005). Since it has been argued that language is in general less lateralized in patients with schizophrenia (Crow, 1997), we predicted similar bilateral activation in schizophrenia patients and relatives, compared with healthy persons, expected to show preeminent activation of left language areas (Baron-Cohen et al., 1997).

2. Methods and materials

2.1. Participants

Two psychiatrists (SMG, EYC) and a psychologist (DDA) assessed all participants, who were seen at the Cognitive Neurology Section and the Psychiatry Department at FLENI Hospital, Buenos Aires. All participants were right-handed and provided written informed consent as approved by the local bioethics committee, and have therefore been performed in accordance with the ethical standards set by the 1964 Declaration of Helsinki.

2.1.1. Patients

Psychiatry outpatients were invited to participate in the study if they (a) had a DSM-IV-TR diagnosis of schizophrenia, any subtype, confirmed with a Composite International Diagnostic Interview (Robins et al., 1988) administered by a consultant psychiatrist (EYC), (b) were aged 18 to 50 years, and (c) had been on the same medications for at least two weeks. Patients reported having been on antipsychotic medications during the whole disease process, i.e., eight years on average (Table 1), but this could not be confirmed with chart review, nor were data available on exposure to typical vs. atypical antipsychotics during that period.Exclusion criteria were (a) misuse or addiction to illegal substances in the previous 6 months, (b) active symptoms having recently (<2 weeks) warranted antipsychotic dose adjustment or admission to the hospital, day hospital, or intensive outpatient treatment, or (c) a history of mental retardation. Current symptom severity was assessed with the Positive and Negative Syndrome Scale (Kay et al., 1987). A total of 14 patients

Table 1
Demographic and clinical data, MATRICS consensus cognitive battery scores, and response latency and accuracy.

	Patients (n = 14)	Siblings (n = 14)	Controls (n = 14)	Statistic	p
Age (years)	30.6 ± 7	30.4 ± 4.8	28.4 ± 8.3	F = 0.475	0.062
Education (years)	14 ± 2	15.1 ± 2.4	15.2 ± 1.8	F = 1.508	0.234
Parental education (years)	11.2 ± 3.6	12.8 ± 3.3	14.4 ± 3.6	F = 2.834	0.071
Women, n (%)	1 (7)	6 (43)	6 (43)	$X^2 = 5.57$	0.357
Age at onset (years)	23.5 ± 4.8				
Disease duration (years)	7.8 ± 4.5				
MMSE score	28.8 ± 1.5	28.9 ± 1.4	29.5 ± 0.9	F = 1.329	0.276
WAT score	32.4 ± 4.3	33.1 ± 5.6	34.6 ± 7.9	F = 0.454	0.638
FRT score	22.7 ± 2.6	24.6 ± 1.9	23.1 ± 4.9	F = 1.262	0.294
MCCB (percentile)					
Speed of processing	4 ± 0[a]	29 ± 26[a]	47 ± 18[a]	F = 17.98	<0.001
Attention/Vigilance	17 ± 21	27 ± 30	53 ± 22[a]	F = 7.815	0.001
Working memory	17 ± 19[b]	38 ± 33	58 ± 26	F = 8.501	0.001
Verbal learning	23 ± 22	32 ± 30	59 ± 24[a]	F = 7.406	0.002
Visual learning	28 ± 29[b]	51 ± 41	65 ± 23	F = 4.774	0.014
Reasoning/Problem solving	24 ± 22	29 ± 29	49 ± 31[a]	F = 7.071	0.002
Social cognition	21 ± 27	32 ± 32	63 ± 26[a]	F = 8.228	0.001
Symptom severity					
PANSS, positive	13.4 ± 6.5				
PANSS, negative	21.6 ± 7.6				
PANSS, total	36.6 ± 11.2				
Hamilton Depression score	6.4 ± 4.3[a]	3.0 ± 3.6	0.9 ± 1.4	F = 9.527	<0.001
Hamilton Anxiety score	8.9 ± 6.3[a]	4.7 ± 4.5	1.5 ± 2.1	F = 8.986	0.001
Medications					
Valproic acid, n (%)	1 (7.1)				
Risperidone, n (%)	5 (35.7)				
Olanzapine, n (%)	3 (21.4)				
Clozapine, n (%)	1 (7.1)				
Quetiapine, n (%)	2 (14.3)				
Paliperidone, n (%)	4 (28.6)				
CMZ equivalent (mg/day)	146.4				
SSRI, n (%)	4 (28.6)				
Promethazine (%)	1 (7.1)				
Biperidene	1 (7.1)				
Clomipramine	1 (7.1)				
Benzodiazepine, n (%)	8 (57.1)				
Response latency (ms)					
BET					
Experimental condition	241 ± 48[b]	218 ± 46	188 ± 44	F = 4.757	0.014
Control condition	189 ± 53[b]	160 ± 40	135 ± 34	F = 5.396	0.009
FToM					
Experimental condition	293 ± 54	273 ± 41	215 ± 53[a]	F = 9.331	<0.001
Control condition	182 ± 42[a]	153 ± 21	127 ± 21	F = 12.01	<0.001
EToM					
Experimental condition	280 ± 54	280 ± 34	248 ± 42	F = 2.388	0.105
Control condition	183 ± 51[b]	158 ± 34	142 ± 32	F = 3.795	0.031
Response accuracy (%)					
BET					
Experimental condition	95 ± 4[b]	97 ± 5	99 ± 2	F = 3.418	0.043
Control condition	98 ± 3	98 ± 5	99 ± 2	F = 0.254	0.777
FToM					
Experimental condition	91 ± 6 [b]	93 ± 7	97 ± 3	F = 3.309	0.047
Control condition	95 ± 3	95 ± 5	97 ± 2	F = 0.254	0.777
EToM					