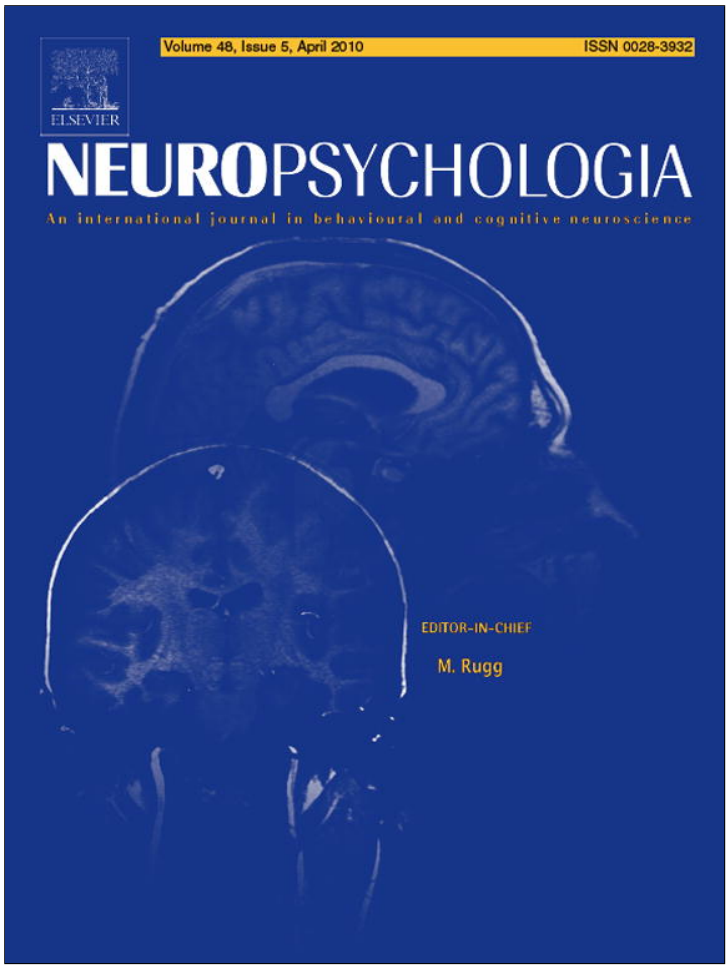

Neuropsychologia 48 (2010) 1209–1215

Contents lists available at ScienceDirect

Neuropsychologia

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

Emotion processing and theory of mind in schizophrenia patients and their unaffected first-degree relatives

Delfina de Achával[a,b], Elsa Y. Costanzo[a], Mirta Villarreal[a,b], Ignacio O. Jáuregui[a], Araceli Chiodi[a], Mariana N. Castro[c], Rodolfo D. Fahrer[a], Ramón C. Leiguarda[a], Elvina M. Chu[d], Salvador M. Guinjoan[a,b,e,*]

[a] Department of Neurology and Psychiatry, Fundación Lucha contra Enfermedades Neurológicas de la Infancia (FLENI), Buenos Aires, Argentina
[b] Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), Argentina
[c] Department of Physiology, University of Buenos Aires School of Medicine, Argentina
[d] Institute of Neurology, University College London, London, United Kingdom
[e] Department of Neurophysiology, University of Buenos Aires School of Psychology, Argentina

ARTICLE INFO

Article history:
Received 11 March 2009
Received in revised form 7 December 2009
Accepted 11 December 2009
Available online 21 December 2009

Keywords:
Social cognition
Endophenotype
Schizophrenia

ABSTRACT

Previous studies have suggested that social cognition is affected in individuals with schizophrenia. The purpose of this study was to explore to what extent social cognition deficits are shared by unaffected first-degree relatives, and the nature of the relationship between performance in different paradigms of social cognition. 20 Schizophrenia patients (7 females, 31 ± 10 years), 20 healthy age- and gender-matched individuals, 20 unaffected first-degree relatives of the schizophrenia patients (11 females, 50 ± 20 years), and 20 healthy individuals matched for age and gender were recruited. Patients showed deficits in the detection of social Faux Pas (0.80 ± 0.17 vs. controls: 0.94 ± 0.09, $p = 0.025$) and the correct identification of Theory of Mind stories (0.71 ± 0.13 vs. controls: 0.82 ± 0.12, $p = 0.038$). Relatives performed poorly in the Faces Test (0.83 ± 0.14 vs. controls: 0.9 ± 0.08, $p = 0.048$), the Reading the Mind in the Eyes Test (0.59 ± 0.17 vs. controls: 0.71 ± 0.14, $p = 0.046$) and the detection of social Faux Pas (0.8 ± 0.2 vs. controls: 0.93 ± 0.09, $p = 0.024$). Abnormalities were independent of age, years of education, and general cognitive performance in patients and their relatives. Performance in an Emotion Processing task (Faces Test) was correlated with performance in theory of mind tests in healthy individuals and relatives of patients with schizophrenia only. These results suggest that schizophrenia patients and their unaffected first-degree relatives display similar but nonidentical patterns of social cognition processing.

1. Introduction

Schizophrenia is characterized by psychotic symptoms such as formal thought disorder, hallucinations, and delusions (American Psychiatric Association, 1994). Although the essential feature of schizophrenia is disruption of the interpersonal world, impaired social functioning frequently precedes the onset of overt psychosis resulting in severe functional loss in different social settings (Kee, Horan, Mintz, & Green, 2004; Penn, Corrigan, Bentall, Racenstein, & Newman, 1997). This has been recognized since the inception of the concept of schizophrenia, thus, in Kraepelin's (1919) words:

> "Frequently the patients have already shut themselves off from their family and surroundings long before the appearance of the more striking symptoms (...), which is connected with a suppression driven to the limit of the possible of all natural emotions."

Over the past decades, most neuropsychiatric studies in schizophrenia have largely focused on disorders of cognitive processes such as executive function, attention, or working memory (Cirillo & Seidman, 2003; Evans, Chua, McKeena, & Wilson, 1997) which may affect patients' psychosocial skills. Only more recently have researchers shifted their attention towards social cognition in schizophrenia (Brüne, 2005; Irani et al., 2006; Penn et al., 1997; Pinkham, Penn, Perkins, & Lieberman, 2003). Social cognition refers to the mental operations underlying social interactions, which include processes involved in perceiving, interpreting, and generating responses to the intentions and emotions of other persons (Adolphs, 2003; Brothers, 1990; Fiske & Taylor, 1991; Kunda, 1999; Ostrom, 1984).

* Corresponding author at: FLENI, Section of Cognitive Neurology & Neuropsychiatry, Montañeses 2325, 8th Floor, C1428AQK Buenos Aires, Argentina.
Tel.: +54 11 5777 3200x2824; fax: +54 11 5777 3209.
E-mail address: sguinjoan@fleni.org.ar (S.M. Guinjoan).

0028-3932/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.neuropsychologia.2009.12.019

Two dimensions of social cognition have received particular attention in the literature, namely Emotion Processing (EP) and Theory of Mind (ToM) (Green, Olivier, Crawley, Penn, & Silverstein, 2005; Penn, Addington, & Pinkham, 2006). EP refers to aspects of perceiving and using emotion, and the empirical knowledge of this aspect of social cognition is usually based in studies of affect perception in faces and eyes (Adolphs, Damasio, Tranel, & Damasio, 1996; Green, Olivier, Crawley, Penn, & Silverstein, 2005). Whereas sometimes it has been considered an EP task, akin to traditional facial emotional recognition paradigms (Fertuck et al., 2009), the Reading the Mind in the Eyes is usually considered a ToM test in that it probes the inference of mental states of others. ToM can be defined as the understanding that others also have minds, with different and separate beliefs, desires, mental states, and intentions from our own (Green et al., 2005; Premack & Woodruff, 1978).

The relationship between EP and ToM has recently been put into question, with some data indicating that these are closely interrelated phenomena (Ochner, 2008). Assessing other persons' intentions necessarily involves the appraisal of their emotional status as well as one's own emotional response to them (Ochner, 2008). This is most evident in tests involving recognition of facial expressions, which are often used in the measurement of either variable (Ochner, 2008).

Initially developed for application in the field of autism (Saxe, Carey, & Kanwisher, 2004), measures of ToM and EP have been extended to schizophrenia, in part because of the similarity between aspects of social dysfunction in autism and schizophrenia (Brüne, 2005; Corcoran, 2001; Frith, 1992). In fact, Frith was the first to suggest that many symptoms associated with schizophrenia could be explained in terms of a compromised ToM (Frith, 1992). Preliminary data suggest that EP and ToM deficits are present in unaffected first-degree relatives of patients with schizophrenia (Aleman, Swart & van Rijn, 2008; Irani et al., 2006) and this may indicate that the performance in ToM tasks is genetically influenced, possibly constituting an endophenotype (Corcoran, 2001; Gottesman & Gould, 2003). More recently, Gur and colleagues have estimated the heritability of emotion processing deficits using a simple, short test of this function (Gur et al., 2007), and attempts have been made to map this important dimension of social cognition to specific chromosomal loci (Almasy et al., 2008; Hill et al., 2008). However, there is a paucity of studies on familial aggregation of social cognitive deficits characteristic of schizophrenia. The few studies that investigate Theory of Mind in unaffected first-degree relatives often offer conflicting results (Janssen, Krabbendam, Jolles, & van Os, 2003; Marjoram et al., 2006). Whereas one study found an association between performance in Theory of Mind tests and genetic liability to schizophrenia (Janssen et al., 2003), another study suggested that Theory of Mind abnormalities were psychotic state-dependent, and not due to genetic traits of schizophrenia (Marjoram et al., 2006).

With regard to EP deficits in unaffected relatives of schizophrenic patients, some studies suggest that this population has similar, although less severe abnormalities than those found in patients (Phillips & Seidman, 2008). However, this has not been a consistent finding. Instead EP deficits may be difficult to separate from general cognitive impairments in patients and their unaffected relatives (Pomarol-Clotet et al., 2009).

Regardless of differences between reports studying individuals affected by schizophrenia and those genetically loaded for it, there are indications that ToM involves an amygdala centred processing system while EP involves the medial prefrontal cortex and superior temporal sulcus (Frith & Frith, 1999; Frith & Frith, 2001), but it is not clear if alterations in these social cognitive abilities have a shared pathophysiology or heritability. Preliminary data indicate that patients with schizophrenia display different correlation patterns for ToM and EP from healthy controls (Brüne, 2005), but to our knowledge this relationship has not been tested in unaffected relatives of schizophrenia patients.

We tested the hypothesis that ToM and EP performance are familial traits; therefore unaffected first-degree relatives of schizophrenia patients might display similar, but less intense abnormalities than patients in ToM and EP performance. Secondly, we sought to determine whether performance in both these dimensions of social cognition showed the same relationship in schizophrenia patients, unaffected first-degree relatives and healthy individuals.

2. Methods

This was a cross-sectional study on the relationship between measures of social cognition in patients with schizophrenia, their unaffected first-degree relatives and healthy control groups.

2.1. Subjects

Two consultant 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, between July 1, 2007 and September 30, 2008. All participants gave 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.

2.2. Patients (P)

Psychiatry outpatients were invited to participate in the study if they (a) received a DSM-IV-TR diagnosis of schizophrenia (any subtype), confirmed with a Composite International Diagnostic Interview (Robins, Wing, Wittchen, & Helzer, 1988) administered by a consultant psychiatrist (EYC), (b) were aged 18–75 years, and (c) had been on the same medications for at least two weeks. Exclusion criteria were (a) misuse or addiction to illegal substances in the previous 6 months, (b) active symptoms having warranted antipsychotic dose adjustment or admission to the hospital, day hospital, or intensive outpatient treatment, in the preceding 2 weeks or (c) a history of mental retardation. Current symptom severity was assessed with the Positive and Negative Syndrome Scale (PANSS; Kay, Fiszbein, & Opler, 1987). Twenty patients with schizophrenia (7 females, age 30.9 ± 10 years, range 19–55 years) were recruited for this study. Two patients were siblings.

2.3. Relatives (R)

First-degree biological relatives of the recruited patients were included from 16 families and consisted of the parents (six mothers, four fathers) and the siblings (five sisters, five brothers), aged 18–75 years, of schizophrenia patients as defined above (age 50.1 ± 19.6 years, range 19–75 years). Exclusion criteria included (a) the lifetime presence of any DSM-IV-TR Axis I psychotic disorder diagnosis as detected by a psychiatric interview with consultant psychiatrist (EYC) and (b) treatment with antipsychotics, antidepressants, or mood stabilizers.

2.4. Controls

Healthy volunteers were recruited from local community attendees to free lectures related to health promotion as advertised in posters and the media, from staff, and colleagues in other institutions. Exclusion criteria included (a) the lifetime presence of any DSM-IV-TR Axis I anxiety, mood, or psychotic disorder diagnosis as detected by a psychiatric interview with a consultant psychiatrist and (b) a medication history of antidepressants, antipsychotics, or mood stabilizers. A schizophrenia patient control group (PC; $n = 20$, 7 females, age 28.2 ± 5.6 years, range 20–47 years) and a first degree relatives control group (RC; $n = 20$, 11 females, age 44.2 ± 17 years, range 25–69 years) were recruited to the study.

2.5. Procedures

2.5.1. Cognitive Screening Tests

All participants were screened for general cognitive impairments with the Mini Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975), Addenbrooke's Cognitive Examination (ACE; Mathuranath, Nestor, Berrios, Rakowicz, & Hodges, 2000), Frontal Assessment Battery (FAB; Dubois, Slachevsk, Litvan, & Pillon, 2000), and Facial Recognition Test (FRT; Benton & Van Allen, 1968). The latter test was used to control for possible impairments in face perception which could interfere with recognition of facial expressions.

2.5.2. Social Cognition Tests

The Spanish version of the Faces Test, Reading the Mind in the Eyes Test, Faux Pas Test and ToM Stories Test as provided by their authors were used.

2.5.3. Emotion Processing Test

2.5.3.1. Faces Test (Baron-Cohen, Wheelwright, & Jolliffe, 1997). The Faces Test consisted of 20 photographs of the face of an actress displaying different facial expressions photographed under controlled and standardized lighting conditions facing forward. Each picture is associated with a choice of two emotions (one correct, one incorrect). The label pairs were selected out of a group of twenty emotions, and were arranged pseudo-randomly. The participants were asked to identify the verbal label that most appropriately described the actor's "thinking or feeling" mental state. Each correct choice scored one point.

2.5.4. Theory of Mind Tests

1. *Reading the Mind in the Eyes Test* (Baron-Cohen, Wheelwright, Hill, Raste, & Plumb, 2001)
   Stimuli consisted of 36 photographs of the eyes of different actors, which were presented one at a time in a fixed order. Each pair of eyes was associated with a choice of four emotion labels. Participants were asked to identify the verbal label that most appropriately described the actor's "thinking or feeling" mental state. Each correct choice scored one point.
2. *Faux Pas Test* (Gregory et al., 2002)
   This test consists of 20 verbal stories, half of which contained a social Faux Pas and half of which did not. The stories were presented one at a time, each on a single page. The text was placed in front of participants and read aloud by the researcher, who then asked a series of questions about the story. We quantified correct detections of unintentional Faux Pas (hits), correct rejects (i.e., detection of non Faux Pas stories), and control questions designed to assess the comprehension of the story were scored according to a system devised by Stone, Baron-Cohen, Young, Calder, and Keane (1998).
3. *ToM Stories Test* (Happé, Brownell, & Winner, 1999; Happé, Malhi, & Checkley, 2001)
   The test consisted of 16 short stories, half of these being stories invoking ToM and the other half referring to physical causation (non-ToM). The ToM stories involved interaction between people and were split into four types, involving double bluff, mistakes, persuasion, or white lies, with two examples of each type. Each ToM story was followed by a question testing ability to make inferences about mental states, usually the actor's intentions. The standard scoring criteria of Happé et al. (1999) and Happé et al. (2001) were applied.

2.6. Statistical analysis

Discrete variables in patients, relatives and controls were compared using a chi-square test. General cognitive performance (as measured by the ACE), age, sex, years of education and parental years of education have all been shown to be potential independent contributors to performance in social cognition tests (Ochner, 2008), and therefore their contribution to social cognition performance was explored by means of a forward stepwise logistic regression analysis. Comparison of social cognition measurements between the groups were carried out with an analysis of covariance (ANCOVA), which incorporated as covariates those factors shown to contribute to performance in different measures of social cognition in the present sample. The relationship between EP and all three measures of ToM in each group was explored with a Pearson's test, followed by a partial correlation test, also incorporating covariates shown to contribute to performance in social cognition as described above. Correlations between tests of social and nonsocial cognition were evaluated with a Pearson's test. All data was analysed using SPSS version 13.0 software (SPSS Inc.). A Bonferroni correction was applied to multiple measurements. Significance was assumed at $\alpha < 0.05$, and all reported results were two-tailed.

3. Results

Table 1 shows the demographic and clinical characteristics of all participants. Both patients and relatives were matched for age and gender to their corresponding control groups (P vs. PC, $p = 0.93$; R vs. RC, $p = 0.556$; one-way ANOVA followed by Tukey's test, Table 1), but subjects in both experimental groups had fewer years of formal education (Table 1). Experimental groups and their respective control groups were similar in terms of performance on FAB, MMSE, and FRT. Although still within normal range, patients attained significantly lower ACE scores than healthy control subjects (Table 1). Results obtained in the healthy control groups were comparable to those obtained in the original description of the test in an English speaking population.

Table 1
Sample characteristics and performance in social cognition tests.

	Patients ($n = 20$)	Patient controls ($n = 20$)	Relatives ($n = 20$)	Relative controls ($n = 20$)	Statistic	p
Age (years)	30.9 ± 10[a]	28.2 ± 5.6[a]	50.1 ± 19.6	44.2 ± 17	$F = 10.68$	<0.001
Education (years)	12.4 ± 1.7[b]	16.5 ± 2.4	11.8 ± 4.9[b]	15.2 ± 4.3	$F = 7.77$	<0.001
Parental education (years)	11.3 ± 4.4[c]	14.4 ± 2.6	10.9 ± 3.9[c]	12.7 ± 3.1	$F = 4.78$	0.004
Female	7(35)	7(35)	11(55)	11(55)	$X^2 = 3.23$	0.357
ACE	87.1 ± 8.7[b]	97 ± 2.2	89.3 ± 12.9	96.3 ± 2.3	$F = 6.42$	<0.001
MMSE	28.9 ± 1.6	29.6 ± 0.9	28.4 ± 2.4	29.7 ± 0.6	$F = 2.29$	0.090
FAB	17 ± 2.5	17.8 ± 0.4	15.5 ± 3.5	17.6 ± 0.7	$F = 2.45$	0.075
FRT	23 ± 2.4	24.7 ± 1.8	21.9 ± 3.0[c]	23.7 ± 2.3	$F = 4.64$	0.006
"Faces" test	17.4 ± 1	18.4 ± 1.2	16.6 ± 2.8[b]	18.1 ± 1.5	$F = 4.146$	0.009
"RME" test	23.5 ± 5.4	27.3 ± 3.8	20.9 ± 6.5[b]	25.5 ± 5.2	$F = 5.263$	0.002
"Faux Pas" test						
Hits	47.7 ± 11.5[c]	56.2 ± 5.5	48 ± 12.9[c]	55.6 ± 6.6	$F = 4.654$	0.005
Rejects	18.6 ± 2.1	19.9 ± 0.4	18.9 ± 2.5	19.7 ± 0.7	$F = 2.891$	0.041
Control questions	36.8 ± 3.4	39 ± 1.1	36.2 ± 4.1[b]	38.6 ± 1.6	$F = 4.705$	0.005
ToM stories test						
ToM stories	11.4 ± 2.1[b]	13 ± 2	12.3 ± 1.9	13.2 ± 1.6	$F = 3.333$	0.024
NonToM stories	11.7 ± 3.3[b]	13.9 ± 2	12.6 ± 2.4	13.9 ± 2.4	$F = 3.384$	0.022
Total score	23 ± 5.3[b]	26.8 ± 3	24.9 ± 4.1	27.1 ± 3.4	$F = 4.264$	0.008
Age at onset (years)	23 ± 6					
Disease duration (years)	9 ± 6					
PANSS, positive subscale	16.3 ± 5.4					
PANSS, negative subscale	24.8 ± 9.3					
Total PANSS	83.8 ± 20.8					
Haloperidol	1(5%)					
Risperidone	9(45%)					
Olanzapine	7(35%)					
Clozapine	3(15%)					
Quetiapine	2(10%)					
SSRI	5(25%)					
Benzodiazepine	9(45%)					

Shown are mean ± standard deviation or number (%). ACE: Addenbrooke's Cognitive Examination; MMSE: Mini-Mental State Examination; FAB: Frontal Assessment Battery; FRT: Facial Recognition Test; RME: Reading the Mind in the Eyes; PANSS: Positive and Negative Symptom Scale; SSRI: Selective Serotonin Reuptake Inhibitor.

[a] Different from relatives and relative controls.
[b] Different from patient controls and relative controls.
[c] Different from patient controls, Tukey's test.

Table 2
Stepwise logistic regression analysis of factors predicting performance in the upper 25% range in tests of social cognition.

	B	S.E.	*p*
"*Faces*" *test*			
Age	−0.110	0.044	0.013
Parental education	−0.118	0.202	0.560
Education	0.145	0.116	0.214
Gender	−1.780	1.312	0.175
ACE	0.183	0.087	0.161
FAB	−0.284	0.249	0.254
"*Reading the Mind in the Eyes*" *test*			
Age	−0.055	0.022	0.012
Parental education	−0.037	0.094	0.692
Education	0.048	0.097	0.621
Gender	−0.799	0.567	0.159
ACE	0.152	0.068	0.024
FAB	0.008	0.190	0.968
"*Faux Pas*" *test*			
Age	0.033	0.029	0.265
Parental education	0.092	0.110	0.401
Education	0.197	0.134	0.141
Gender	0.510	0.799	0.523
ACE	0.036	0.052	0.487
FAB	0.294	0.284	0.300
"*ToM Stories*" *test*			
Age	0.030	0.026	0.238
Parental education	−0.127	0.100	0.207
Education	0.193	0.111	0.083
Gender	0.885	0.699	0.206
ACE	0.117	0.058	0.041
FAB	0.556	0.376	0.139

ACE: Addenbrooke's Cognitive Examination Test; FAB: Frontal Assessment Battery. *B*: Coefficient, S.E: standard error.

Patients with schizophrenia showed deficits in the detection of social Faux Pas and incorrect identification of ToM and Physical Causation stories compared to controls (Table 1). Relatives of patients with schizophrenia performed poorly in the Faces Test, the Reading the Mind in the Eyes Test, and in the detection of social Faux Pas. This group also performed worse than healthy controls in the memory-based questions of this test (Table 1).

Age and ACE score were independent predictors of performance in the Reading the Mind in the Eyes Test, whereas years of formal education, parental education, gender and FAB score did not independently predict performance in this test (Table 2). None of the factors predicted performance in the Faux Pas Test. ACE score was an independent predictor of performance in the ToM Stories Test, whereas years of education was marginally predictive of performance in this test (Table 2).

Fig. 1 shows performance in Faces and Reading the Mind in the Eyes tasks (top), Faux Pas Test (middle), and ToM Stories Test (bottom) in schizophrenia patients, their first-degree relatives, and their corresponding healthy comparison groups, after controlling for the influence of age, years of formal education, and general cognitive performance as per logistic regression analysis results. In all cases the proportion of correct responses is depicted. After controlling for these confounders, relatives of patients with schizophrenia showed a deficit in the identification of emotions and mental states in faces and eyes, whereas patients with schizophrenia did not differ from comparable healthy subjects (Fig. 1, top panel). Both schizophrenia patients and their unaffected first-degree relatives showed poor performance in the detection of social Faux Pas, another measure of Theory of Mind, although performance in the memory-based control questions was also deficient in relatives when compared with healthy individuals (Fig. 1, middle panel). Patients performed worse than controls in the ToM Stories Test, due to a deficit in the identification of physical causation but not in the ToM stories themselves (Fig. 1, bottom panel). Relatives of

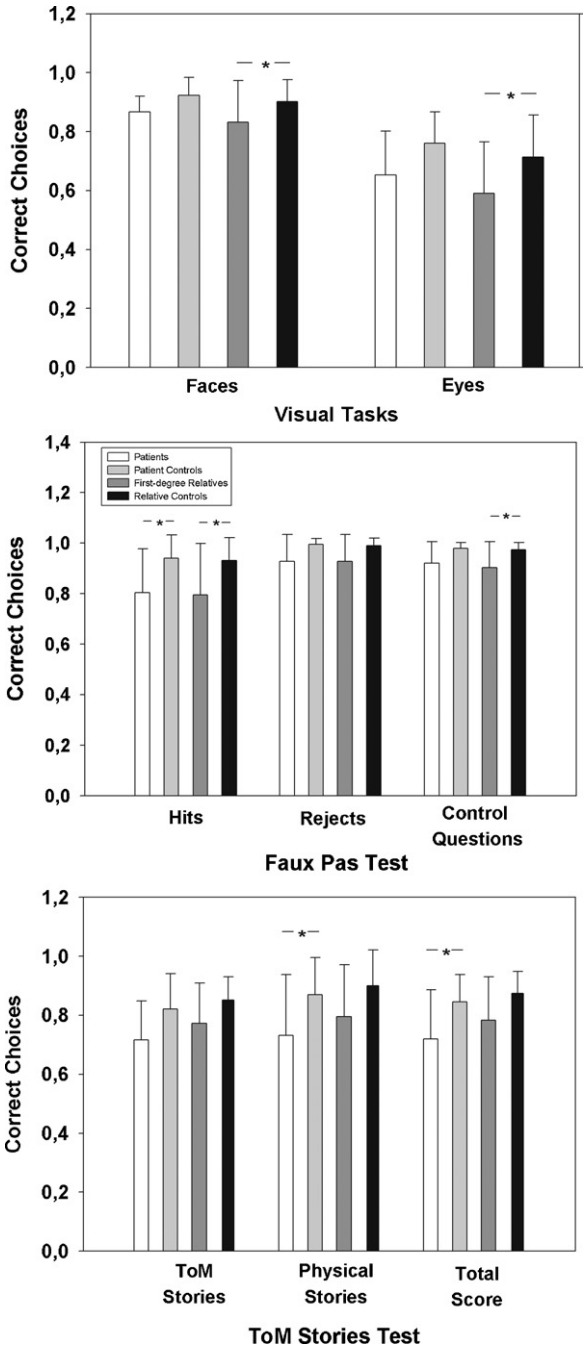

Fig. 1. Performance of patients with schizophrenia, their nonpsychotic first-degree relatives, and healthy individuals matched to either group, on Faces and Reading the Mind in the Eyes Tests (top), Faux Pas Test (middle), and ToM Stories Test (bottom). $^{*}p < 0.05$ vs. healthy controls, ANCOVA followed by Tukey's post hoc test. See the text for details.

schizophrenia patients performed similarly to comparable healthy controls in the ToM Stories Test (Fig. 1, bottom panel).

Emotion processing (EP) did not correlate with any of the three ToM measures in patients with schizophrenia, whereas in unaffected first degree relatives, EP performance was correlated with both Reading the Mind in the Eyes Test ($r = 0.678$, $p = 0.001$) and Faux Pas Test ($r = 0.814$, $p < 0.001$); only the latter association remained significant after controlling for age, cognitive performance, and years of education ($r = 0.567$, $p = 0.018$). Among healthy participants, EP was significantly correlated with the Reading the Mind in the Eyes Test ($r = 0.479$, $p = 0.002$), even after controlling for the aforementioned covariates ($r = 0.355$, $p = 0.031$).

Table 3
Correlation between tests of social and nonsocial cognition.

	"Faces" test	"Reading the Mind in the Eyes" test	"Faux Pas" test	"ToM Stories" test
Patients				
FRT	−0.256, 0.275	0.159, 0.502	0.372, 0.107	0.121, 0.621
FAB	−0.046, 0.847	**0.564**, **0.010**	0.549, 0.012	0.380, 0.108
ACE	−0.070, 0.769	0.442, 0.051	0.200, 0.397	0.279, 0.248
Relatives				
FRT	**0.629**, **0.003**	**0.558**, **0.011**	**0.754**, **<0.001**	0.395, 0.084
FAB	**0.567**, **0.009**	**0.649**, **0.002**	**0.516**, **0.020**	0.210, 0.215
ACE	**0.753**, **<0.001**	**0.800**, **<0.001**	**0.647**, **0.002**	**0.448**, **0.047**
Healthy individuals				
FRT	0.253, 0.116	0.251, 0.119	−0.022, 0.893	−0.010, 0.951
FAB	0.192, 0.234	0.043, 0.793	0.205, 0.205	0.019, 0.908
ACE	**0.607**, **<0.001**	0.291, 0.069	0.240, 0.136	0.179, 0.268

Shown are Pearson's *r*, *p* value. ACE: Addenbrooke's Cognitive Examination; FAB: Frontal Assessment Battery; FRT: Facial Recognition Test.
Significant correlations are shown in bold.

With regard to the relationship between different measurements of ToM, only Faux Pas Test and Reading the Mind in the Eyes Test were found to correlate with each other in patients ($r = 0.478$, $p = 0.033$), their unaffected relatives ($r = 0.679$, $p = 0.001$), and healthy individuals ($r = 0.407$, $p = 0.009$). Reading the Mind in the Eyes Test correlated significantly with ToM Stories Test in unaffected relatives only ($r = 0.451$, $p = 0.046$), and the two verbal tests correlated with each other in patients only ($r = 0.539$, $p = 0.017$).

In the patient group, no significant correlations were observed between different scores on the PANSS scale (negative, positive, total) and scores obtained in the Faces Test, Reading the Mind in the Eyes Test, Faux Pas Test, or ToM Stories Test.

Table 3 shows the correlation between tests of social cognition and measures of general cognitive abilities in patients with schizophrenia, their unaffected relatives, and healthy individuals. In patients, FAB score correlated with performance in the Reading the Mind in the Eyes Test. Among healthy subjects, ACE score correlated with the Faces test score. General cognition assessed by ACE correlated with all measures of social cognition in unaffected relatives of schizophrenia patients, whereas FAB and FRT correlated with the Faces test, the Reading the Mind in the Eyes Test, and the Faux Pas Test as well (Table 3).

4. Discussion

The main findings of this study are that (1) patients with schizophrenia display specific deficits in Theory of Mind, which are independent of other potential predictors in this test, and (2) unaffected first-degree relatives of schizophrenia patients show deficits in both Emotion Processing and Theory of Mind that partially overlap with those seen in schizophrenia patients, and are not explained by the influence of general cognitive difficulties, years of education, and age.

Regarding Theory of Mind tests, in patients with schizophrenia, our results are in partial agreement with previous indications that this disorder is characterized by a deficit in the capacity to attribute mental states to others (Brüne, 2005; Frith, 1992; MacCabe, Leudar, & Antaki, 2004; Pinkham et al., 2003; see Penn, Sanna, & Roberts, 2008 for a review). However, performance in the Emotion Processing test (Baron-Cohen et al., 1997), was similar between patients and healthy individuals, an unexpected finding in view of previous studies demonstrating impaired Emotion Processing in individuals with schizophrenia (Kington, Jones, Watt, Hopkin, & Williams, 2000; Phillips & Seidman, 2008; Pomarol-Clotet et al., 2009). A potential explanation for this result is that our patients belonged to a different population (i.e. stable chronic schizophrenia) than those of previous studies. The present results support the notion that Emotion Processing abnormalities are a heritable trait given their consistent presence in unaffected first-degree relatives, although not independent of clinical status, since no significant deficits were seen in the present sample of treated patients.

As stated before, there are conflicting results in the literature regarding the presence of Emotion Processing and Theory of Mind abnormalities in individuals at genetic risk for schizophrenia. The current study supports the view that Theory of Mind abnormalities depend to some extent on the paradigm used to test this aspect of social cognition.

Unaffected first-degree relatives have abnormal Emotion Processing and worse performance than healthy controls in two out of three Theory of Mind paradigms, suggesting that familial traits are fairly specific and do not encompass the whole range of abnormalities seen in the schizophrenia syndrome. The Faux Pas Test was the only test that showed abnormalities in both patients and relatives even after controlling for significant covariates, therefore emerging as a potential endophenotype of schizophrenia.

The present study found an association between the Faces Test (an EP task) and the Reading the Mind in the Eyes Test (a ToM test) in both healthy individuals and unaffected first-degree relatives of schizophrenia patients, even after controlling for variables associated with performance in social cognition (i.e. age, education, and general cognitive performance). In addition, the Faces Test correlated with the Faux Pas Test (a ToM test) in unaffected relatives. This lends support to the view that EP and ToM are closely related concepts and correct appraisal of the intentions and feelings of others necessitates an intact ability to discern their emotions (Ochner, 2008). The lack of association in the present sample of individuals with schizophrenia is intriguing and is currently the subject of an ongoing study in the functional cerebral correlates (using functional magnetic resonance imaging, fMRI) of performance in different social cognition tasks. Regarding the relationship among the different measures of ToM used here, the present study found a consistent relationship across all experimental groups between Faux Pas Test and Reading the Mind in the Eyes Test. This supports the concept that Reading the Mind in the Eyes evaluates the same construct as the Faux Pas Test. The ToM Stories Test was not consistently related to the other two ToM tests across groups. It remains to be seen if these findings were due to insufficient power to detect the relationship in the present sample or whether ToM Stories Test measures a related, albeit different dimension of social cognition.

There was no correlation between tests of social cognition and severity of symptoms, in contrast with a previous study (Kelemen et al., 2005) which reported an inverse relationship between performance in the Eyes Test and negative symptom severity. At least two reasons could account for this difference. Firstly, our sample was

smaller and might have lacked power to detect the significant correlation. Secondly, patients in our sample were more symptomatic than those in the study by Kelemen et al. (2005), in which almost a third of patients were in remission after at least four weeks off antipsychotics. In addition, most social cognitive tests were correlated with measures of general cognitive ability in unaffected relatives of schizophrenia patients in this study. This does not necessarily reflect causation, because social cognitive performance in this group of relatives remained significantly lower than that of comparable healthy persons even after controlling for general cognitive deficits. Nonetheless, this finding emphasises the need to carefully consider the influence of basic cognitive abilities in social cognitive function in individuals at genetic risk for schizophrenia, in patients and even in healthy people, as a modest correlation between a social and a nonsocial cognitive task was found in the latter group as well (Phillips & Seidman, 2008; Pomarol-Clotet et al., 2009).

Potential clinical implications of the present findings are twofold. Firstly, abnormalities of social cognition detected herein may explain some well-known deficits in social behaviour evident in patients with schizophrenia, which are extendable to individuals who are at genetic risk. Because schizophrenia patients are impaired in monitoring their own self-generated actions and linking these to their own intentions (Frith, Blakemore, & Wolpert, 2000; Shergill, Samson, Bays, Frith, & Wolpert, 2005; Spence, Brooks, Hirsch, Liddle, Meehan & Grasby, 1997), they are additionally impaired in applying pragmatic rules of conversation and it can be predicted that they also have difficulty planning and carrying out social behaviours (Brüne, 2003; Brunet, Sarfati, & Hardy-Bayle, 2003; Sarfati, Hardy-Baylé, Nadel, & Chevalier, 1997; Schmitt & Grammer, 1997). Whereas different studies have examined the relationship between social cognitive deficits and actual social functioning in patients with schizophrenia (Bora, Eryavuz, Kayahan, Sungu, & Veznedaroglu, 2006; Brüne, Abdel-Hamid, Lehmkämper, & Sonntag, 2007; Schenkel, Spaulding, & Silverstein, 2005), further studies are warranted in their unaffected relatives, because their early detection might be useful to predict if those at genetic risk are more liable to develop the full-blown psychotic syndrome. Secondly, partial overlap of deficits in social cognition between schizophrenia patients and their unaffected first-degree relatives suggest that such abnormalities might be (at least partly) inherited. We found support for the initial hypothesis that relatives of schizophrenia patients are deficient in some aspects of social cognition. This suggests that such deficits may be an integral part of the familial vulnerability to the illness, and supports the hypothesis that certain social cognition paradigms can be considered candidates to constitute a neuropsychological endophenotype of schizophrenia (Gottesman, McGuffin, & Farmer, 1987; Portin & Alanen, 1997).

The main limitation of this study was the lack of matching for education level and wide age distribution in the patient's relatives group. The healthy comparison samples were matched for gender and age, but not for years of education in subjects with schizophrenia and their relatives. Another potential limitation is that we did not specifically screen patients' relatives for personality disorders or autism, which may have accounted for social cognition deficits observed in this group. Cluster A personality disorders are known to be overrepresented among individuals with increased genetic risk for schizophrenia. It is also difficult to make definitive conclusions about emotion processing in patients with schizophrenia and their first-degree relatives with just one measure of EP.

In summary, this study shows that unaffected first-degree relatives of schizophrenia patients display patterns of social cognition, which are different from patients and healthy control subjects. It is not clear whether differences in performance between schizophrenia patients and their relatives represent different degrees of functional compromise, such that general cognitive deficits affect specific aspects of social cognition in the patient group. The present results underscore the need to carefully consider how general cognitive abilities affect social cognition in schizophrenia, and suggest that further studies (with first-episode patients, and prospective follow-up over several years) are needed to fully characterise this relationship.

Acknowledgments

DDA is a research fellow from CONICET. MNC is now a PGY-III Psychiatry Resident at the University of Buenos Aires Hospital "José de San Martín". Funding was provided by Agency of Scientific Promotion (grant PICT-2007-01643 SMG) SDG. We are grateful to Ms. María E. Martín for her technical assistance, and Dr. Maarten Milders and Dr. Bruno Wicker for their comments on the first draft of this manuscript.

References

Adolphs, R. (2003). Cognitive neuroscience of human social behaviour. *Nature Reviews—Neuroscience*, *4*, 165–178.
Adolphs, R., Damasio, H., Tranel, D., & Damasio, A. R. (1996). Cortical systems for the recognition of emotion in facial expressions. *The Journal of Neuroscience*, *16*, 7678–7687.
Aleman, A., Swart, M., & van Rijn, S. (2008). Brain imaging, genetics and emotion. *Biological Psychology*, *79*, 59–69.
Almasy, L., Gur, R. C., Haack, K., Cole, S. A., Calkins, M. E., Peralta, J. M., et al. (2008). A genome screen for quantitative trait loci influencing schizophrenia and neurocognitive phenotypes. *American Journal of Psychiatry*, *165*(9), 1185–1192.
American Psychiatric Association. (1994). *Diagnosis and statistical manual of mental disorders* (4th ed.). Washington, DC: American Psychiatric Press.
Baron-Cohen, S., Wheelwright, S., Hill, J., Raste, Y., & Plumb, I. (2001). The 'Reading the mind in the eyes' Test revised version: A study with normal adults, and adults with Asperger Syndrome or High-Functioning autism. *Journal of Child Psychology and Psychiatry*, *42*, 241–252.
Baron-Cohen, S., Wheelwright, S., & Jolliffe, T. (1997). Is there a "language of the eyes"? Evidence from normal adults and adults with autism or Asperger syndrome. *Visual Cognition*, *4*, 311–331.
Benton, A. L, & Van Allen, M. W. (1968). Impairment in facial recognition in patients with cerebral disease. *Cortex*, *4*, 344–358.
Bora, E., Eryavuz, A., Kayahan, B., Sungu, G., & Veznedaroglu. (2006). Social functioning, theory of mind and neurocognition in outpatients with schizophrenia; mental state decoding may be a better predictor of social functioning than mental state reasoning. *Psychiatry Research*, *145*, 95–103.
Brothers, L. (1990). The neural basis of primate social communication. *Motivation and Emotion*, *14*, 81–91.
Brüne, M. (2003). Theory of mind and the role of IQ in chronic disorganized schizophrenia. *Schizophrenia Research*, *60*, 57–64.
Brüne, M. (2005). Emotion recognition, "theory of mind" and social behavior in schizophrenia. *Psychiatry Research*, *133*, 135–147.
Brüne, M., Abdel-Hamid, M., Lehmkämper, & Sonntag, C. (2007). Mental state attribution, neurocognitive functioning, and psychopathology: What predicts poor social competence in schizophrenia best? *Schizophrenia Research*, *92*, 151–159.
Brunet, E., Sarfati, Y., & Hardy-Bayle, M. (2003). Reasoning about physical causality and others' intentions in schizophrenia. *Cognitive Neuropsychiatry*, *8*, 129–139.
Cirillo, M. A., & Seidman, L. J. (2003). Verbal declarative memory dysfunction in schizophrenia: From clinical assessment to genetics and brain mechanisms. *Neuropsychology Review*, *13*, 43–77.
Corcoran, R. (2001). Theory of mind and schizophrenia. In P. W. Corrigan, & D. L. Penn (Eds.), *Social cognition and schizophrenia* (pp. 149–174). Washington, DC: American Psychological Association.
Dubois, B., Slachevsk, A., Litvan, I., & Pillon, B. (2000). The FAB: A frontal assessment battery at bedside. *Neurology*, *55*(11), 1621–1626.
Evans, J. J., Chua, S. E., McKenna, P. J., & Wilson, B. A. (1997). Assessment of a dysexecutive syndrome in schizophrenia. *Psychological Medicine*, *27*, 1101–1112.
Fertuck, E. A., Jekal, A., Song, I., Wyman, B., Morris, M. C., Wilson, S. T., et al. (2009). Enhanced "Reading the Mind in the Eyes" in borderline personality disorder compared to healthy controls. *Psychological Medicine*, *22*, 1–10.
Fiske, S. T., & Taylor, S. E. (1991). *Social cognition* (2nd ed.). New York: McGraw-Hill Book Co.
Folstein, M. F., Folstein, S., & McHugh, P. R. (1975). Mini-Mental State: A practical method for grading the cognitive state of patients for the clinicians. *The Journal of the American Society for Psychical Research*, *12*(3), 189–198.
Frith, C. D. (1992). *The cognitive neuropsychology of schizophrenia*. Hove, UK: Laurence Erlbaum Associates.
Frith, C. D., Blakemore, S., & Wolpert, D. M. (2000). Explaining the symptoms of schizophrenia: Abnormalities in the awareness of action. *Brain Research Review*, *31*, 357–363.

Frith, C. D., & Frith, U. (1999). Interacting minds—A biological basis. *Science*, *286*, 1692–1695.
Frith, U., & Frith, C. D. (2001). The biological basis of social interaction. *Current Directions in Psychological Science*, *10*, 151–155.
Gottesman, I. I., & Gould, T. D. (2003). The endophenotype concept in psychiatry: Etymology and strategic intentions. *American Journal of Psychiatry*, *160*(4), 636–645.
Gottesman, I. I., McGuffin, P., & Farmer, A. E. (1987). Clinical genetics as clues to the real genetics of schizophrenia (a decade of modest gains while playing for time). *Schizophrenia Bulletin*, *13*, 23–47.
Green, M. F., Olivier, B., Crawley, J. N., Penn, D. L., & Silverstein, S. (2005). Social cognition in schizophrenia: Recommendations from the measurement and treatment research to improve cognition in schizophrenia new approaches conference. *Schizophrenia Bulletin*, *31*, 882–887.
Gregory, C., Lough, S., Stone, V., Erzinclioglu, S., Martin, L., Baron-Cohen, S., et al. (2002). Theory of mind in patients with frontal variant frontotemporal dementia and Alzheimer's disease: Theoretical and practical implications. *Brain*, *125*(Pt. 4), 752–764.
Gur, R. E., Nimgaonkar, V. L., Almasy, L., Calkins, M. E., Ragland, J. D., Pogue-Geile, M. F., et al. (2007). Neurocognitive endophenotypes in a multiplex multigenerational family study of schizophrenia. *American Journal of Psychiatry*, *164*(5), 813–819.
Happé, F., Brownell, H., & Winner, E. (1999). Acquired "theory of mind" impairments following stroke. *Cognition*, *70*, 211–240.
Happé, F., Malhi, G. S., & Checkley, S. (2001). Acquired mind-blindness following frontal lobe surgery? A single case study of impairment "theory of mind" in a patient treated with stereotactic anterior capsulotomy. *Neuropsychologia*, *39*, 83–90.
Hill, S. K., Harris, M. S. H., Herbener, E. S., Pavuluri, M., & Sweeney, J. A. (2008). Neurocognitive allied phenotypes for schizophrenia and bipolar disorder. *Schizophrenia Bulletin*, *34*(4), 743–759.
Irani, F., Platek, S. M., Panyavin, I. S., Calkins, M. E., Kohler, C., Siegel, S. J., et al. (2006). Self-face recognition and theory of mind in patients with schizophrenia and first-degree relatives. *Schizophrenia Research*, *88*(1–3), 151–160.
Janssen, I., Krabbendam, L., Jolles, J., & van Os, J. (2003). Alterations in theory of mind in patients with schizophrenia and non-psychotic relatives. *Acta Psychiatrica Scandinavica*, *108*(2), 110–117.
Kay, S. R., Fiszbein, A., & Opler, L. A. (1987). The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophrenia Bulletin*, *13*, 261–276.
Kee, K. S., Horan, W. P., Mintz, J., & Green, M. F. (2004). Do the siblings of schizophrenia patients demonstrate affect perception deficits? *Schizophrenia Research*, *67*(1), 87–94.
Kelemen, O., Erdélyi, R., Pataki, I., Benedek, G., Janka, Z., & Kéri, S. (2005). Theory of mind and motion perception in schizophrenia. *Neuropsychology*, *19*(4), 494–500.
Kington, J. M., Jones, L. A., Watt, A. A., Hopkin, E. J., & Williams, J. (2000). Impaired eye expression recognition in schizophrenia. *Journal of Psychiatric Research*, *34*(4–5), 341–347.
Kraepelin, E. (1919). In G. M. Robertson (Ed.), *Dementia praecox and paraphrenia. Translated by Barclay RM (1971)*. New York: Robert E Krieger.
Kunda, Z. (1999). *Social cognition: Making sense of people*. Cambridge, MA: MIT Press.
MacCabe, R., Leudar, I., & Antaki, C. (2004). Do people with schizophrenia display theory of mind deficits in clinical interactions? *Psychological Medicine*, *34*(3), 401–412.
Marjoram, D., Job, D. E., Whalley, H. C., Goutouna, V. E., McIntosh, A. M., Simonotto, E., et al. (2006). A visual joke fMRI investigation into Theory of Mind and enhanced risk of schizophrenia. *Neuroimage*, *31*(4), 1850–1858.
Mathuranath, P. S., Nestor, P. J., Berrios, G. E., Rakowicz, W., & Hodges, J. R. (2000). A brief cognitive test battery to differentiate Alzheimer's disease and frontotemporal dementia. *Neurology*, *55*, 1613–1620.
Ochner, K. N. (2008). The social–emotional processing stream: Five constructs and their translational potential for schizophrenia and beyond. *Psychiatry*, *64*(July (1)), 48–61.
Ostrom, T. M. (1984). The sovereignty of social cognition. In R. S. Wyner, & T. K. Skrull (Eds.), *Handbook of social cognition* (pp. 1–37). Hillsdale, NJ: Earlbaum.
Penn, D. L., Addington, J., & Pinkham, A. (2006). Social cognitive impairments. In J. A. Lieberman, T. S. Stroup, & D. O. Perkins (Eds.), *American psychiatric association textbook of schizophrenia*. Arlington: American Psychiatry Publishing Press.
Penn, D. L., Corrigan, P. W., Bentall, R. P., Racenstein, J. M., & Newman, L. (1997). Social cognition in schizophrenia. *Psychological Bulletin*, *121*, 114–132.
Penn, D. L., Sanna, L. J., & Roberts, D. L. (2008). Social cognition in schizophrenia: An overview. *Schizophrenia Bulletin*, *34*(3), 408–411.
Phillips, L. K., & Seidman, L. J. (2008). Emotion processing in persons at risk for schizophrenia. *Schizophrenia Bulletin*, *34*(5), 888–903.
Pinkham, A. E., Penn, D. L., Perkins, D. O., & Lieberman, J. A. (2003). Implications of a neural basis for social cognition for the study of schizophrenia. *American Journal of Psychiatry*, *160*, 815–824.
Pomarol-Clotet, E., Hynes, F., Ashwin, C., Bullmore, E. T., McKeena, P. J., & Laws, K. R. (2009). Facial emotion processing in schizophrenia: A non-specific neuropsychological deficit? *Psychological Medicine*, (September), 1–9.
Portin, P., & Alanen, Y. O. (1997). A critical review of genetic studies of schizophrenia. Epidemiological and brain studies. *Acta Psychiatrica Scandinavica*, *95*, 1–5.
Premack, D. L., & Woodruff, G. (1978). Does the chimpanzee have a theory of mind? *The Behavioral and Brain Sciences*, *1*, 515–526.
Robins, L. N., Wing, J., Wittchen, H. U., & Helzer, J. E. (1988). The composite International Diagnostic Interview. An epidemologic instrument suitable for use in conjunction with different diagnostic systems and in different cultures. *Archives of General Psychiatry*, *45*, 1067–1077.
Sarfati, Y., Hardy-Baylé, M. C., Nadel, J., Chevalier, J. F., & Widlocher, D. (1997). Attribution of mental states to others in schizophrenic patients. *Cognitive Neuropsychiatry*, *2*, 1–17.
Saxe, R., Carey, S., & Kanwisher, N. (2004). Understanding other minds: Linking developmental psychology and functional neuroimagining. *Annual Review of Psychology*, *55*, 87–124.
Schenkel, L. S., Spaulding, W. D., & Silverstein, S. M. (2005). Poor premorbid social functioning and theory of mind deficit in schizophrenia: Evidence of reduced context processing? *Journal of Psychiatric Research*, *39*(2005), 499–508.
Schmitt, A., & Grammer, K. (1997). Social intelligence and success: Don't be too clever in order to be smart. In A. Whiten, & R. W. Byrne (Eds.), *Machiavellian intelligence. II. Extensions and evaluations* (pp. 86–111). Cambridge, MA: Cambridge University Press.
Shergill, S., Samson, G., Bays, P. M., Frith, C. D., & Wolpert, D. M. (2005). Evidence for sensory prediction deficits in schizophrenia. *American Journal of Psychiatry*, *162*, 2384–2386.
Spence, S. A. B., Brooks, D. J., Hirsch, S. R., Liddle, P. F., Meehan, J., & Grasby, P. M. (1997). A PET study of voluntary movement in schizophrenic patients experiencing passivity phenomena (delusions of alien control). *Brain*, *120*, 1997–2011.
Stone, V. E., Baron-Cohen, S., Young, A. W., Calder, A. J., & Keane, J. (1998). Impairments in social cognition following orbitofrontal or amygdala damage. *Abstracts—Society for Neuroscience*, *24*, 1176.