Journal of Psychiatric Research xxx (2014) 1–10

Contents lists available at ScienceDirect

Journal of Psychiatric Research

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

Pattern of brain activation during social cognitive tasks is related to social competence in siblings discordant for schizophrenia

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ARTICLE INFO

Article history:
Received 9 December 2013
Received in revised form
13 May 2014
Accepted 13 May 2014

Keywords:
fMRI
Schizophrenia
Siblings
Social skills
Lateralization
Hemispheric dominance

ABSTRACT

Measures of social competence are closely related to actual community functioning in patients with schizophrenia. However, the neurobiological mechanisms underlying competence in schizophrenia are not fully understood. We hypothesized that social deficits in schizophrenia are explained, at least in part, by abnormally lateralized patterns of brain activation in response to tasks engaging social cognition, as compared to healthy individuals. We predicted such patterns would be partly heritable, and therefore affected in patients' nonpsychotic siblings as well. We used a functional magnetic resonance image paradigm to characterize brain activation induced by theory of mind tasks, and two tests of social competence, the Test of Adaptive Behavior in Schizophrenia (TABS), and the Social Skills Performance Assessment (SSPA) in siblings discordant for schizophrenia and comparable healthy controls ($n = 14$ per group). Healthy individuals showed the strongest correlation between social competence and activation of right hemisphere structures involved in social cognitive processing, whereas in patients, the correlation pattern was lateralized to left hemisphere areas. Unaffected siblings of patients exhibited a pattern intermediate between the other groups. These results support the hypothesis that schizophrenia may be characterized by an abnormal functioning of nondominant hemisphere structures involved in the processing of socially salient information.

1. Introduction

In spite of a lifetime prevalence below 1%, schizophrenia is the eighth leading cause of disability adjusted life years (DALY) in adults younger than 35 years of age worldwide (Murray and Lopez, 1996; World Health Organization, 1996). This occurs in spite of widespread availability of antipsychotic treatment. Social competence is compromised before the onset and after the treatment of acute symptoms of schizophrenia, and accounts for a significant proportion of disability and poor social functioning outcomes (Harvey et al., 2012). Social functioning and social cognition deficits are present in unaffected siblings of patients in most studies and have therefore been proposed to be genetically determined and thus considered potential endophenotypes of the disease (Walshe et al., 2007; Baas et al., 2008; de Achával et al.,

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http://dx.doi.org/10.1016/j.jpsychires.2014.05.011
0022-3956/

2010; de Achával et al., 2012; see Martin et al., 2013 and Lavoie et al., 2013 for reviews). The heritable neurobiological underpinnings of social dysfunction in schizophrenia are, however, unsettled. In accordance with theories of schizophrenia which propose disease symptoms are originated in abnormalities resulting in an abnormal developmental brain "torque" (e.g., Mitchell and Crow, 2005), we and others have observed right-hemisphere activation deficits during social cognitive tasks in siblings discordant for schizophrenia (Das et al., 2012; de Achával et al., 2012; Goldschmidt et al., 2014). Specifically, we observed that patients and their unaffected siblings tend to activate mostly left cerebral structures associated with theory of mind when challenged with basic emotion processing and "reading the mind" tasks involving human faces; healthy individuals were shown to activate approximately equivalent left and right structures under such conditions (de Achával et al., 2012). In at-risk subjects, certain clinical traits have a relationship with both faulty activation of the right temporoparietal junction and actual social competence (Goldschmidt et al., 2014). Thus, among nonpsychotic siblings of patients with schizophrenia, we observed that cluster B personality traits were associated with both a pattern of brain activation induced by social cognitive tasks similar to that seen in schizophrenia (i.e., faulty nondominant hemisphere activity) and dysfunctional social competence characteristic of the full-blown syndrome (Goldschmidt et al., 2014). Whereas inheritance of the disease possibly results from an adverse combination of several common gene variations with small penetrance, it has also been proposed that genetic alterations resulting in abnormal brain lateralization may contribute significantly to important dimensions of the disease (Priddle and Crow, 2013). Such studies refer mostly to language functions. The latter have been demonstrated to be relevant to overall neurocognitive functioning and therefore social competence in schizophrenia (Sullivan et al., 2013). Moreover, we have recently advanced the hypothesis that faulty language functions of the nondominant hemisphere could be a factor explaining social dysfunction in this disease, by impairing the choice of the semantically appropriate term for socially relevant emotions (de Achával et al., 2012).

In this study, we sought to establish if there exists a relationship between patterns of brain activation during social cognition tasks and social competence, which has a well-documented, direct relationship with actual social functioning (Bowie et al., 2006; Green et al., 2012). The primary hypothesis of the study was that impairments in the activation of right hemisphere brain structures during theory of mind tasks underlie, in part, the social difficulties faced by schizophrenia subjects in their daily living, and therefore would be related to the severity of social competence deficits in these patients. We also hypothesized that such abnormal lateralization pattern is in part heritable, and therefore we included a sample of relatives of patients with schizophrenia. We further reasoned that the pattern of relationship between activation of right hemisphere brain structures involved in social cognition and actual social competence would be similar in relatives – albeit less severe – to that seen in patients, on the basis of partially shared genetic predisposition to the disease. The study of this group of relatives may also be of interest because nonpsychotic siblings of patients with schizophrenia are not exposed to the potentially confounding influences of psychopharmacological agents in brain activation, nor do they suffer from active psychotic symptoms interfering with general neurocognitive abilities, in turn affecting functional MRI results. To confirm this, we also assessed general neurocognitive abilities in all groups, in addition to social competence performance.

2. Methods and materials

2.1. Subjects

This was a case–control observational study on the association between brain activation during social cognitive tasks and performance in social competence tests, conducted in a sample of participants described in detail in prior reports (de Achával et al., 2012; de Achaval et al., 2013; Goldschmidt et al., 2014). Briefly, the study sample consisted of 14 patients with schizophrenia, 14 nonpsychotic siblings of schizophrenia patients, and 14 healthy controls, who were evaluated at the Cognitive Neurology Section and the Psychiatry Department at FLENI Hospital, Buenos Aires. Before starting the study, all participants read and signed an informed consent form, according to the norms of the 1964 Declaration of Helsinki, and approved by the local bioethics committee acting as a human subjects panel. A legal representative of patients was also asked to provide written consent as per the panel's recommendation in agreement with local regulations.

Patients with a DSM-IV-TR schizophrenia diagnosis and stable clinical status were invited to participate (de Achával et al., 2012; de Achaval et al., 2013). Diagnosis was confirmed by means of the Composite International Diagnostic Interview (Robins et al., 1988); this diagnostic tool was employed with patients only, and was not applied to their nonpsychotic siblings or healthy controls. Clinical stability was defined as a period of two consecutive weeks with no need for medication changes, admission to the hospital, or transition to an intensive outpatient treatment or day hospital.

We included siblings of patients participating in the study ($n = 8$) and siblings of patients who did not meet the clinical stability criteria or were unable to participate ($n = 6$). Moreover, they did not fulfill criteria for any DSM-IV-TR Axis I psychotic disorder diagnosis, and were not receiving any antipsychotics, antidepressants, or mood stabilizers (Goldschmidt et al., 2014).

The control group was comprised of healthy subjects, from the local area. The exclusion criteria were the same as for siblings. In addition, patients with anxiety or mood disorders were not included.

Presence of affective disorders was ascertained in the same clinical interview, prior go the administration of cognitive and social functioning tests, and MRI sessions. Participants were asked to provide their history of contacts with mental health professionals, psychiatric admissions, and use of antidepressants and anxiolytics, and were administered a Beck depression inventory (Table 1).

2.2. Neurocognitive testing

For basic neurocognitive screening, participants were administered the Mini Mental State Examination (MMSE) (Folstein et al., 1975). The Word Accentuation Test (WAT) (Del Ser et al., 1997) was used to estimate premorbid intelligence.

Detailed characterization of cognitive status in all participants was performed with the MATRICS Consensus Cognitive Battery (MCCB) (Kern et al., 2008; Nuechterlein et al., 2008) as described elsewhere (de Achával et al., 2012).

2.3. Social competence testing

Test of Adaptive Behavior in Schizophrenia (TABS) (Velligan et al., 2007): this test was designed to assess underlying abilities needed to complete goal-directed adaptive behavior such as initiation, planning and sequencing, and problem identification. The TABS test is comprised of 6 test areas including medication management (the person is asked to fill a medication container based upon instructions of the doctors and to remember to call for a new

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Table 1
Demographic and clinical data, SSPA and TABS scores, EToM and BET performance.

	Patients ($n = 14$)	Siblings ($n = 14$)	Controls ($n = 14$)	F	P
Age (years)	30.6 [7.0]	30.4 [4.8]	28.4 [8.3]	0.475	0.625[a]
Education (years)	14.0 [2.0]	15.1 [2.4]	15.2 [1.8]	1.508	0.234[a]
Parental education (years)	11.2 [3.6]	12.8 [3.3]	14.4 [3.6]	2.642	0.071[a]
Female	1 [7]	6 [43]	6 [43]		0.080[b]
MCCB Total	25.4 [12.6][c]	38.1 [15.5][c]	52.9 [6.2][c]	18.202	<0.001[a]
Speed	3.8 [10.0][c]	28.6 [26.1][c]	47.3 [18.2][c]	17.979	<0.001[a]
Attention	17.3 [21.4][c]	27.1 [29.5]	53.0 [22.4][c]	7.815	0.001[a]
Working Memory	17.1 [18.6][d]	37.5 [33.1]	58.3 [25.7]	8.501	0.001[a]
Verbal Learning	22.8 [21.6]	32.4 [30.2]	58.6 [23.9][c]	7.406	0.002[a]
Visual Learning	27.9 [29.2][d]	50.6 [40.7]	64.8 [23.4]	4.774	0.014[a]
Problem Solving	13.5 [21.9]	24.4 [21.5]	48.7 [31.3][c]	7.071	0.002[a]
Social Cognition	20.8 [26.8]	32.4 [32.3]	63.0 [25.8][c]	8.228	0.001[a]
WAT	32.4 [4.3]	33.1 [5.6]	34.6 [7.9]	0.454	0.638[a]
BDI score	15.2 [10.7][c]	3.1 [5.1]	3.1 [4.5]	12.04	<0.001[a]
Age at onset (years)	23.5 [4.8]				
Disease duration (years)	7.8 [4.5]				
PANSS. positive subscale	13.4 [6.5]				
PANSS. negative subscale	21.6 [7.6]				
Total PANSS	71.7 [21.1]				
Risperidone	5 [36]				
Paliperidone	5 [36]				
Olanzapine	2 [14]				
Clozapine	1 [7]				
Valproate	1 [7]				
Quetiapine	3 [21]				
SSRI	6 [43]				
Benzodiazepine	9 [64]				
Social skills					
SSPA	49.0 [13.5][c]	62.9 [13.2][c]	77.6 [7.3][c]	21.038	<0.001[a]
TABS	16.8 [2.4]	20.0 [2.8]	19.3 [7.9]	1.449	0.247[a]
BET					
Response latency (ms)					
Experimental condition	2410 [480][c]	2180 [460]	1880 [440]	4.757	0.014[a]
Control condition	1890 [530][c]	1600 [400]	1350 [340]	5.396	0.009[a]
Response accuracy (%)					
Experimental condition	95 [4][c]	97 [5]	99 [2]	3.421	0.043[a]
Control condition	98 [3]	98 [5]	99 [2]	0.254	0.777[a]
EToM					
Response latency (ms)					
Experimental condition	2800 [540]	2800 [340]	2480 [420]	2.388	0.105[a]
Control condition	1830 [51][c]	1580 [34]	1420 [32]	3.795	0.031[a]
Response accuracy (%)					
Experimental condition	88 [5]	88 [6]	91 [5]	1.903	0.163[a]
Control condition	84 [3]	85 [3]	85 [4]	0.549	0.582[a]

Shown are mean [SD] for continuous variables or number [%] for discrete variables. BDI: Beck Depression Inventory; BET: basic emotion task; EToM: theory of mind task-eyes; MCCB: MATRICS Consensus Cognitive Battery (numbers shown is the percentile); SSPA: Social Skills Performance Assessment; TABS: Test of Adaptive Behavior in Schizophrenia; SSRI: Selective serotonin reuptake inhibitor; WAT: Word Accentuation Task.

[a] ANOVA followed by Tukey HSD.

[b] Fisher's exact test.

[c] Tukey HSD showed statistically significant differences with the other two groups.

[d] Tukey HSD showed statistically significant differences only with control group.

prescription at a specific time), empty bathroom (the person is asked what would be needed to stock an empty bathroom in order to get ready everyday), shopping skills (the person is asked how they would get to the store by using a map, to remember a grocery list, and to pay for items with a set amount of money), clothes closet (the person is asked to select appropriate clothing for specific activities), work and productivity (the person is asked to make packets of flyers and stack them for mailing), and social skills (basic skills such as voice volume and eye contact are rated during the test by the evaluator). Scores are obtained for each subtest and the total score reflect the percent correct. Higher scores indicate better adaptive functioning.

Social Skills Performance Assessment (SSPA, Patterson, 2001): this test is a social role-play task in which the subject participates in two 3-min selected social problem situations. These role-plays (scenes) are acted out between an interviewer and the participant, and are audiotaped for subsequent scoring. The SSPA interviewers (DDA, MGG) were blind to psychiatric ratings, described below, which were performed during the same visit by different clinical personnel. These raters performed alternately the interview and independently rated participants' responses. Inter-rater agreement in ratings after a training session, in 10 individuals, was at least .9 in all cases.

2.4. fMRI tasks

We used a set of paradigms described in detail elsewhere (de Achával et al., 2012). Briefly, a set of photographs containing a face with an emotional expression was presented to the subjects. The presentation was organized in 14 blocks of 25 s having 4 photographs each; additionally for each face two simultaneous words were presented. In the experimental blocks the words express two alternative emotions or mental states, and subject were asked to press a button to indicate which of the two words best described the mental state of the photographed person. In the control blocks, subjects were presented the same stimuli as in the target condition but were asked to indicate which of the two simultaneously presented words best described the gender of the photographed person. Thus, the key difference between the two conditions was the type of judgment the subject had to make. The blocks were presented alternately and the order of the faces was randomized.

There were two types of stimuli. In the basic emotion task (BET), we used photographs from the Picture of Facial Affect (Ekman and Friesen, 1976). The stimulus portrays the whole face in a close-up, black and white photograph expressing basic emotions (angry, happy, sad, etc.; see de Achával et al., 2012 for examples of stimuli). In the theory of mind task-eyes (EToM) task, we used a modified version of the 'Reading the Mind in the Eyes' Test (Baron-Cohen et al., 1999). The stimuli portray only the eyes in close-up, black and white photographs, but in this case the expressions correspond to complex mental states such us jealous, enthusiastic, threatened, etc. (see de Achával et al., 2012 for examples of stimuli).

Each photograph was presented for 5 s and was followed by a 0.75-s interval in which the screen was blank. Correct words were counterbalanced to left and right side of the screen. All the stimuli were presented via Presentation®. Subjects were trained with an example of each task before scanning. The tasks were presented in a counterbalanced order, half of the subjects starting with the BET task and the other half taking the EToM first. In the original paradigm, a ToM in whole faces task (FToM) was administered after BET or EToM; brain activation results in this task were similar to EToM (de Achával et al., 2012), therefore only BET and EToM were considered for the present analyses. There was a short break between tasks but the subject did not leave the scanner or move between tasks.

2.5. fMRI data acquisition

MRI data were acquired on a 3 T GE HDx scanner with an 8 channel head coil. Change in blood-oxygenation-level-dependent

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(BOLD) T2* signal was measured using a gradient echo-planar imaging (EPI) sequence. Thirty contiguous slices were obtained in the AC-PC plane (TR: 2.37 s, TE: 30 ms, flip angle: 90°, FOV: 24 cm, 64 × 64 pixels per inch matrix, voxel size = 3.75 × 3.75 × 4). A structural MRI was acquired with the fast SPGR–IR sequence (120 slices, 1 mm thick slices, TR 7.876 ms, TE 2.984 ms, flip angle 12°, FOV 24 cm, 256 × 256 matrix). Two sessions of 155 volumes were taken per subject.

2.6. Analysis of behavioral data

Discrete variables in patients, siblings and controls were compared using a chi-square test, and continuous variables were compared using a one-way ANOVA followed by a Tukey HSD test. Significance was assumed at an $\alpha = 0.05$, and all reported results were two-tailed. All tests were performed with the SPSS version 13.0 software (SPSS Inc.), and adjusted for multiple comparisons.

2.7. fMRI analysis

2.7.1. Individual image processing

Image processing was carried out using SPM5 (Wellcome Department of Cognitive Neurology, London, UK) implemented in MATLAB 7 (Mathworks Inc., Sherborn, MA, USA). Slice-timing correction was applied to each volume. The imaging time series was realigned to the first volume and spatially normalized to the stereotactic space of Talairach and Tournoux (1988) using Montreal Neurological Institute reference brain (Ashburner and Friston, 1999). The coordinates showed in Tables are in the MNI system. The normalized volumes of $2 \times 2 \times 2$ mm^3 were spatially smoothed by an isotropic Gaussian kernel of 8 mm at full width half-maximum (Friston et al., 2000).

Individual analysis was computed using the general linear model including the experimental (EMOTION) and control (GENDER) conditions. The design matrix also included correction for head movements. We did not detect group differences in head movements prior to correction. The effects were modeled using a boxcar function convolved with a canonical hemodynamic response function to create regressors of interest. A linear contrast EMOTION–GENDER was applied to the design matrix of each subject.

2.7.2. Regression analysis

For each group of subjects: controls, patients, and siblings, we performed a regression analysis implementing the first level *t* contrast EMOTION–GENDER and used the SSPA or TABS scores as a regressor. This would yield a single brain map for each paradigm (BET or EToM) showing which brain areas concerned with basic emotion or theory of mind processing are related to performance in the social functioning tasks (i.e., two brain maps, one for each test paradigm). For this operation we used a statistical threshold (uncorrected) of $p < 0.001$ combined with an extended cluster size threshold of 10 voxels.

2.7.3. Correlations in regions of interest

Based on the random effect results reported previously (de Achával et al., 2012), we selected three different pairs of regions of interest (ROIs): 1) left inferior frontal gyrus (IFG), defined as a sphere centered at (−45, 18, 2), and right IFG centered at (40, 24, 2); 2) left middle frontal gyrus (MFG) at (−48, 15, 26), and right MFG at (48, 15, 26), and 3) left superior temporal gyrus (STG) at (−51, −45, 3), and right STG at (51, −45, 3). These ROIs have been implicated in different studies to be involved in diverse aspects of the processing of social cognitive information, including motor phenomena involving mirror neurons presumably helping with the processing of facial features, theory of mind, and the choosing of the appropriate noun to designate the observed emotion, mental status, or intention (see de Achával et al., 2012 for a full description of this circuit). All ROIs were spheres of 10 mm radius built using MarsBar algorithm. The selection of the MNI coordinates was based in the overlapping of active clusters for the three groups within Brodman's areas 44–45, 9 and 22 respectively. Signal percent changes within each ROI were calculated for every subject in the EMOTION–GENDER contrast.

These data were entered in a correlation analysis to establish the relation between the brain mean % activity for ROI and the social functioning score in the SSPA and TABS test. We used the SPSS 13.0© for the statistical analysis with a significant threshold of $p < 0.05$.

2.7.4. Lateralization of brain activation

In order to check for laterality effects we computed a whole brain laterality index measure from the regression analysis (Seghier, 2008). The index (LI) was assessed by counting the number of voxels that survive the used threshold multiplied by the sum of the *t* values of those voxels within the left (LH) and the right (RH) hemispheres. So the formula was:

$$\mathrm{LI} = \frac{N_L{*}t_L - N_R{*}t_R}{(N_L{*}t_L + N_R{*}t_R)} \quad (1)$$

where N_L and N_R account for the number of active voxels above the specified threshold for the left and the right hemisphere respectively, and t_L and t_R account for the sum of *t* values of the corresponding voxels.

Additionally, the laterality index was obtained within the ROIs in order to establish correlations to performance in SSPA and TABS in each group. In this case the index was calculated as $(L-R)/(L+R)$, being *L* the sum of LEFT % signal change in all three ROIs in both conditions, and *R* the sum of RIGHT % signal change in all three ROIs in both conditions. A Pearson correlation coefficient was used.

3. Results

3.1. Behavioral results

Patients with schizophrenia, unaffected siblings, and healthy controls were comparable in terms of age, sex, years of education, years of parental education, general intelligence, and basic cognitive screening performance (Table 1). While not statistically significant, the proportion of men tended to be higher among patients, and education level lower in parents of siblings discordant for schizophrenia. As previously described (de Achával et al., 2012; de Achaval et al., 2013), patients had lower performance than controls in various neurocognitive dimensions as assessed in greater detail by means of the MCCB, a battery designed for the detection of specific cognitive deficits in schizophrenia patients (Table 1). Nonpsychotic siblings occupied an intermediate situation between patients and healthy controls in regards to most measures of neurocognitive functioning; their performance was significantly lower than that in healthy individuals in processing speed, attention, verbal learning, problem solving, and social cognition, yielding a lower global MCCB score in this group (Table 1).

Performance in all participants was between 80% and 100% of accuracy in the two tasks carried out during fMRI scanning. Patients with schizophrenia showed significantly less accurate responses than healthy controls in the BET task ($p = 0.033$). During the EToM task, groups did not differ significantly regarding accuracy of performance. Siblings did not show significant performance differences when compared to either healthy persons or patients with

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schizophrenia (Table 1). There were no significant relationships between performance in the social cognitive tasks in the fMRI paradigm and performance in the social competence tasks.

3.2. Whole brain regression

In healthy persons, no significant correlations were observed between brain activation patterns during social cognitive tasks and performance in the SSPA social functioning task. In patients with schizophrenia, greater left temporoparietal activation during the BET and EToM tasks were significantly associated with better SSPA performance. In nonpsychotic siblings of patients, activation in bilateral prefrontal areas and insula during BET, and left prefrontal and left anterior cingulate activation during EToM both correlated with SSPA performance (Fig. 1, Table 2).

In controls, activation of areas in the left parietal lobe, right insula and right superior temporal gyrus during both BET and EToM tasks correlated with social competence as assessed by the TABS. Activation of the right IFG during EToM was also related to social competence as assessed with the TABS. In patients, correlation between brain activation during EToM and TABS performance was observed in right posterior cingulum left parietal lobule, left superior temporal gyrus, as well as in the right superior frontal area. Bilateral prefrontal and anterior cingulate activation during EToM correlated with TABS performance in healthy siblings of schizophrenia patients. Areas of left prefrontal cortex in this group that correlated with TABS and SSPA were remarkably similar (Fig. 1, Table 2). On the other hand, there is no clear overlap of whole brain correlation regions in the three groups.

The laterality index for the significant correlations was obtained by the Equation (1). The index for controls, BET vs. TABS was −0.56, and EToM vs. TABS of −0.38, where the negative value indicates a right tendency. In siblings BET vs. SSPA gave an index of 0.17, EToM vs. SSPA of 0.55 and EToM vs. TABS of 0.87, all positive values indicating a left tendency. For patients, the indexes were 0.2 for BET vs. SSPA; 0.93 for EToM vs. SSPA and −0.31 for EToM vs. TABS, indicating a mixed tendency depending on the cognitive task. According with previous literature about laterality index (Seghier, 2008), LI < −0.2 is considered right dominance, −0.2 < LI < 0.2 bilateral behavior and LI > 0.2 left dominance. Thus, healthy controls showed a complete right dominance, while siblings and patients showed a mixed dominance, bilateral for BET vs. SSPA and left dominance for EToM vs. SSPA. EToM vs. TABS was predominantly left for siblings and right for patients.

Table 2
Brain areas modulated by the social functioning tasks. Shown are coordinates in the MNI system.

	Peak activation			Cluster volume (n voxels)	t value
	x	y	z		
Patients BET vs SSPA					
L superior temporal gyrus	−34	−64	16	27	4.6
R fusiform gyrus	34	−50	−10	21	5.03
Patients EToM vs SSPA					
L superior temporal gyrus	−60	−24	6	65	5.78
Siblings BET vs SSPA					
L dorsolateral prefrontal cortex	−40	48	2	92	7.07
R dorsolateral prefrontal cortex	38	46	2	63	6.26
L insula	−32	24	−6	47	4.3
R insula	38	26	−6	10	4.21
Siblings EToM vs SSPA					
L superior frontal gyrus	−20	50	30	14	5.24
R superior frontal gyrus	16	24	58	37	4.41
L cingulate gyrus	−8	30	36	56	5.2
L middle frontal gyrus	−32	36	24	55	5.01
Controls BET vs TABS					
R insula	40	−36	28	38	5.23
L paracentral lobule	−18	−40	56	16	4.98
R superior temporal gyrus	54	−72	14	13	4.94
Controls EToM vs TABS					
R precuneus	18	−56	28	869	8.86
R superior temporal gyrus	38	−50	22	294	5.11
L inferior parietal lobule	−46	−36	66	10	5.28
R fusiform gyrus	36	−54	−8	27	4.86
R inferior frontal gyrus	36	34	2	44	4.69
Patients EToM vs TABS					
R cingulate gyrus	10	−26	42	2727	10.61
L superior parietal lobule	−34	−42	66	216	5.28
L inferior parietal lobule	−46	−28	30	36	5.83
R superior frontal gyrus	26	24	40	109	5.39
L superior temporal gyrus	−62	−18	4	76	4.33
Siblings EToM vs TABS					
L middle frontal gyrus	−30	36	20	78	5.82
L cingulate gyrus	−4	28	36	197	4.95
R medial frontal gyrus	14	34	32	13	4.17

3.3. Correlations in regions of interest

Fig. 2 depicts plots of correlations between activation in ROIs and social competence performance in the three experimental groups. In healthy individuals, social competence as assessed with the TABS, was related to activation of the right inferior and middle frontal gyri during EToM (IFG: Pearson's $r = 0.58$, $p = 0.02$; MFG: Pearson's $r = 0.56$, $p = 0.03$). In contrast, in patients with

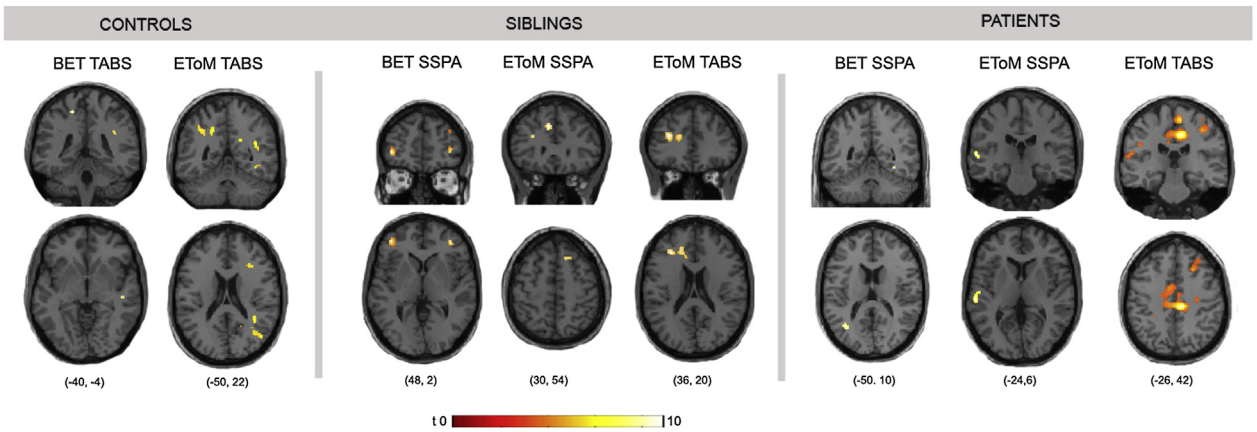

Fig. 1. Regression analysis between the first level t contrast EMOTION−GENDER and SSPA or TABS scores. Significant correlations at $p < 0.001$ uncorrected are shown for controls (left panel), siblings (middle panel) and patients (right panel). Numbers below each photo indicate the (y,z) coordinates of the planes.

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schizophrenia, activation of the left STG during the BET test was related to performance in the TABS ($r = 0.57$, $p = 0.03$), whereas greater activation in the right middle frontal gyrus during EToM was associated with poorer performance in the SSPA ($r = -0.61$, $p = 0.02$). Bilateral activation of the inferior frontal gyrus (coinciding with Broca's area) during BET, was associated with greater SSPA performance in siblings of patients with schizophrenia (RIFG: $r = 0.64$, $p = 0.01$; LIFG: $r = 0.6$, $p = 0.02$).

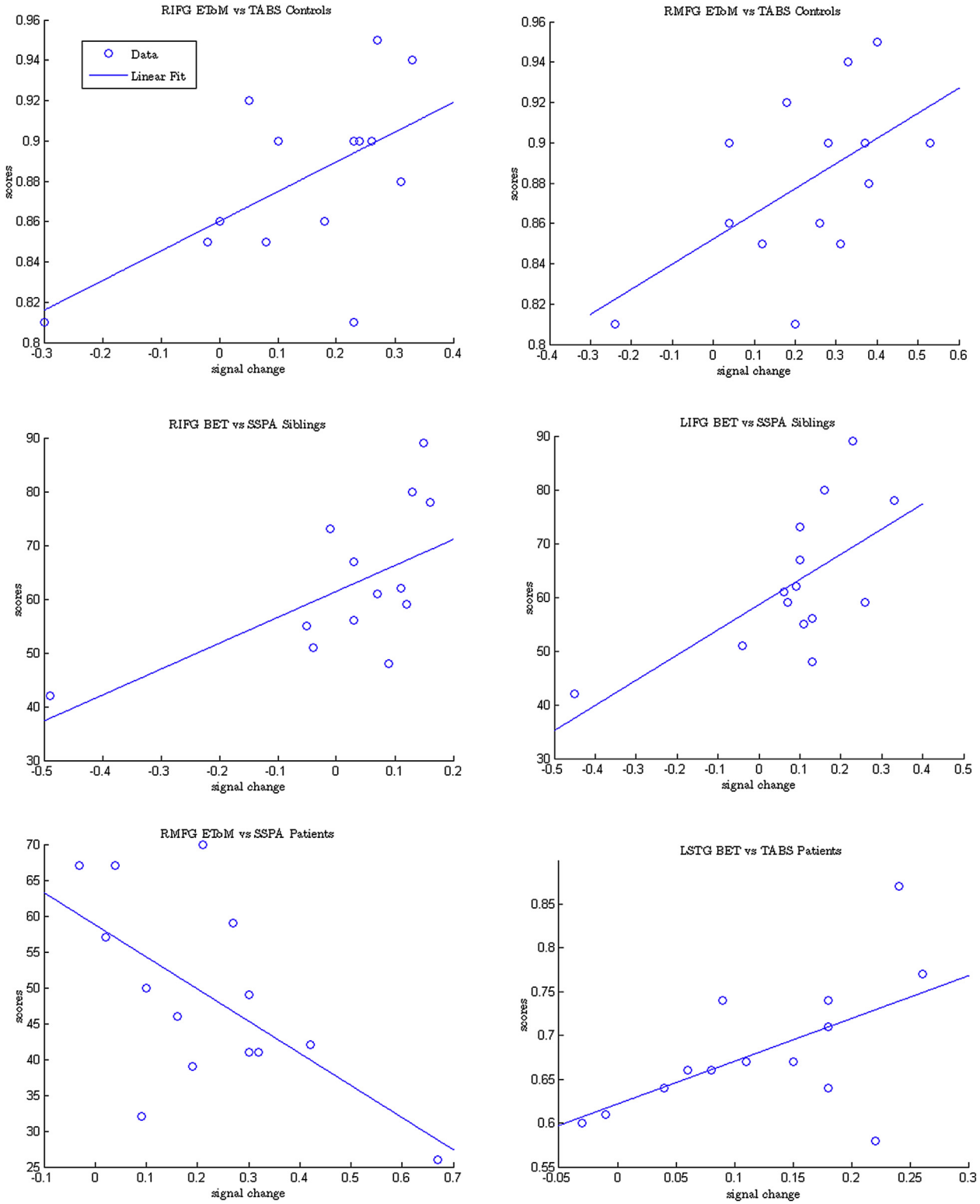

Fig. 2. ROIs correlations with SSPA and TABS scores. Significant correlations at $p < 0.05$ are shown for controls (top panel), siblings (middle panel) and patients (bottom panel). Please see the text for details. BET: Basic Emotion Task; EToM: Theory of Mind Task-Eyes; TABS: Test of Adaptive Behavior in Schizophrenia; SSPA: Social Skills Performance Assessment; RIFG: Right Inferior Frontal Gyrus; RMFG: Right Mid Frontal Gyrus; LIFG: Left Inferior Frontal Gyrus; LSTG: Left Superior Temporal Gyrus.

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We observed a significant laterality effect across groups ($F = 4.22$, $p = 0.022$). The *post hoc* analysis revealed that the only significant difference was controls vs. patients (delta = 46.07, $p = 0.018$), i.e. healthy controls displayed greater relative activity in the right ROIs, and patients with schizophrenia exhibited more left hemispheric activity. Differences of nonpsychotic siblings with healthy controls and schizophrenia patients were 21.35 and 24.71, respectively. The direction of the difference revealed a gradient in ROI lateralization from right hemisphere to left ROI activation in the following order: healthy controls − siblings − patients.

In line with this, the laterality index correlated positively with performance in SSPA in patients ($R = 0.58$, $p = 0.039$; Fig. 3) − i.e., increasing performance in SSPA with greater left ROIs activity. There were no other statistically significant correlations between laterality index and SSPA or TABS in each group.

4. Discussion

The main finding of this study is the observation of a relationship between brain activity induced by social cognitive tasks and actual social competence, different in healthy persons and siblings discordant for schizophrenia. Healthy individuals showed the strongest correlation between right-hemisphere structures involved in social cognition, and social competence as assessed with either TABS or SSPA. Patients with schizophrenia, on the other hand, displayed the strongest correlation between left-hemisphere activation and social competence (along with an inverse relationship for right-hemisphere activation and performance in the TABS), and unaffected siblings of schizophrenia patients exhibited an intermediate pattern between the two other groups, with right and left hemisphere activation associated with performance in either social competence test.

This observation provides support for the primary hypothesis of the study, namely that abnormal activation of right hemisphere brain structures in the processing of social cognitive information in schizophrenia is related to poor social competence, and thus presumably partly underlies patients' deficits in actual daily functioning. There is emerging evidence in the last decade that, instead of being a "left-hemisphere" disorder (Crow, 1997), schizophrenia may be characterized by an abnormal functioning of nondominant hemisphere structures (Mitchell and Crow, 2005) normally involved in the processing of socially salient information, including emotion processing and theory of mind (Decety and Lamm, 2007). The brain network subserving social cognitive phenomena in normal conditions has been the subject of much research in the last decade (e.g., see Decety and Lamm, 2007, for a review). In general, studies coincide in assigning much importance to the right temporoparietal junction as pivotal in the organization of theory of mind processing, as probed in the present study. Interestingly, brain areas whose activation was found in the present study to correlate with social competence coincide in part with brain areas previously shown to display significant activation by social cognitive tasks especially in healthy individuals, namely right medial frontal gyrus and right superior temporal sulcus/temporoparietal junction (see Fig. 1 and de Achával et al., 2012). There is no such clear overlap in siblings discordant for schizophrenia, further pointing to faulty or alternate brain processing underlying social competence in these groups. Our group and others (de Achával et al., 2010; Ross and Monnot, 2011; Das et al., 2012) have obtained evidence that performance in the naming of mental states is compromised in patients with schizophrenia and at-risk subjects, whereas activation of right hemisphere brain structures presumably involved in mirror neuron and theory of mind function is also faulty in both of these groups (Das et al., 2012; de Achával et al., 2012). However, to our knowledge, no previous study has documented a relationship between specific patterns of brain activity evoked by social cognitive tasks, and actual social competence in schizophrenia patients and at-risk subjects. While not demonstrating causation, the present results document a relationship between faulty right-hemisphere activation during social cognitive tasks and poor social competence in siblings discordant for schizophrenia which may represent a neurobiological signature of social deficits in these groups. Although not identical to those seen in patients with schizophrenia, abnormalities in their nonpsychotic

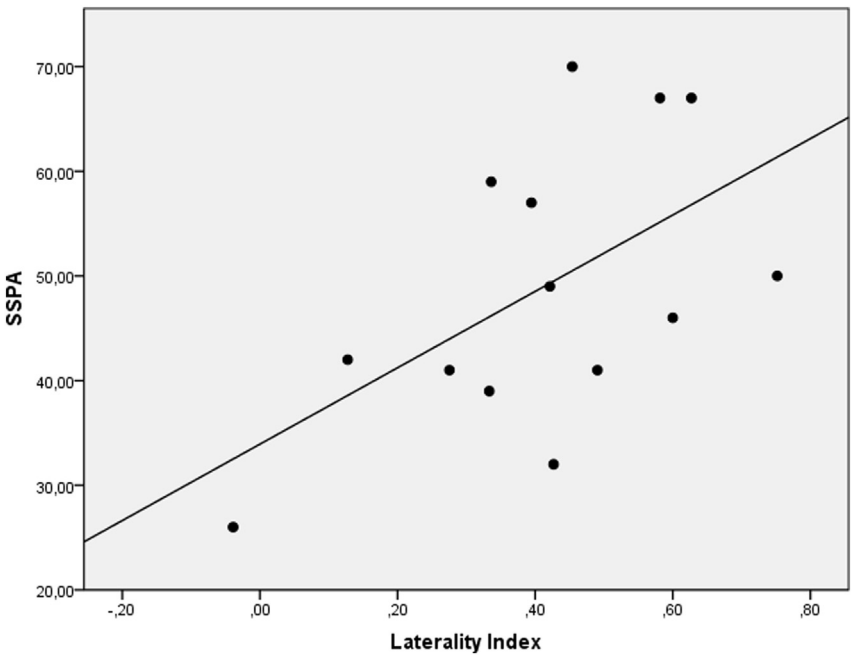

Fig. 3. Brain activation laterality index $[(L-R)/(L+R)]$ correlation with SSPA in patients. $R = 0.58$, $p = 0.039$. Performance in the test of social competence was related to greater activation of left hemisphere structures involved in social cognition during emotion processing/theory of mind tasks. Please see the text for details.

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siblings add to previous evidence which points to social cognitive deficits as an endophenotype of schizophrenia (Lavoie et al., 2013; Martin et al., 2013). The relationships observed between brain activity evoked by social cognitive tasks and actual social competence, also provide a heuristically valuable framework for the appropriate interpretation of two sets of previous observations in these groups of subjects: those documenting a faulty right-hemisphere activation in siblings discordant for schizophrenia compared with healthy subjects (de Achával et al., 2012; Goldschmidt et al., 2014), and observations on faulty social competence in patients with schizophrenia and their nonpsychotic siblings related to deficits in both social cognition and general neurocognitive abilities (de Achával et al., unpublished results). An important additional point should be made to help the interpretation of the present results. Inherent in the correlation analyses is the fact that reported results do not permit to make inferences regarding absolute values of brain activation. Previous observations in this regard (de Achával et al., 2012; Goldschmidt et al., 2014) actually indicate that left hemisphere activation tends to be greater than right hemisphere activation in all groups; differences in the relationship of such brain activation with social competence suggest that in siblings discordant for schizophrenia, neurobiological mechanisms underlying social competence are different from those in healthy individuals – i.e. the latter rely more in nondominant hemisphere activity than the other groups.

The present results can be interpreted in light of the pioneering work of Ross and coworkers (Ross et al., 2001; Ross and Monnot, 2011). These authors demonstrated that linguistic abnormalities in patients with schizophrenia are indistinguishable from those of patients with right-hemisphere lesions, and distinct from speech disorders characteristic of a variety of dominant, left-hemisphere lesions. Using a paradigm investigating aprosodia, these authors demonstrated that schizophrenia is characterized by an asymmetric process in which language deficits are represented mainly in the right, rather than the left hemisphere. They were able to predict that schizophrenia patients not only displayed aprosodia, but that they would also display difficulties in the processing of facial affect, ultimately resulting in deficits in interpersonal relationships and social isolation. Apart from previous evidence from our group and others confirming these predictions (de Achával et al., 2012), the present results show a direct relationship between right-hemisphere activation deficits in the processing of socially salient information, and actual deficits in social competence. In addition, Ross' specific prediction of faulty functioning of right posterior Sylvian cortices has been confirmed in recent observations using fMRI paradigms of emotional processing and theory of mind (de Achával et al., 2012). Whereas these authors documented prosodic deficits in spoken language, we propose that faulty right-hemisphere functioning could also result in semantic deficits specifically affecting words denoting emotional and social content (de Achával et al., 2010). This is in line with Crow's proposal (e.g., Berlim et al., 2003) of abnormal brain lateralization accounting for certain positive symptoms of schizophrenia, specifically Schneiderian first-rank symptoms. We suggest such deficits might also involve appraisal of social situations in the form of an anomia for emotionally-laden words, thus explaining negative symptoms of schizophrenia referred to social life, as well.

In light of these observations, we propose that faulty activation in schizophrenia of the right middle frontal gyrus (involved, with other structures including some in the left hemisphere, in mirror neuron activity necessary for accurate interpretation of another person's affective facial gestures, e.g., Said et al., 2011) and right temporoparietal junction critical in theory of mind abilities, (e.g., Decety and Lamm, 2007) ultimately results, via abnormal input to Wernicke's area in the dominant hemisphere, in difficulties with the accurate naming of emotions and mental states in others, rendering the patient unable to interpret with precision the meaning of different social situations and thus compromising his/her ability to perform in daily activities (Weed et al., 2010; Tompkins, 2012). We are currently exploring the possibility that deficits of activation of right hemispheric structures, involved in mirror neuron activity and theory of mind, be due to actual structural deficits in those areas, by means of voxel-based morphometry.

The question arises of what are the mechanisms of abnormal brain lateralization in schizophrenia as explaining a series of its clinical features, including social disability. Recent research on the genetic basis of the psychoses (e.g. Purcell et al., 2009) maintain that predisposition to schizophrenia is highly polygenic, probably involving single nucleotide polymorphisms (SNPs) in thousands of genes, each with very small individual effect, and highly prevalent in the general population. However, our study and previous evidence on abnormal brain lateralization show that aspects of the disease that are highly relevant to the deficits seen in this disorder could be accounted for by the single genetic variable of laterality/asymmetry (Priddle and Crow, 2013). In this respect, the present findings are supported by other neuroradiological research (e.g., Bhojraj et al., 2011; Byun et al., 2012; Li et al., 2012). In this regard, the fact that nonpsychotic siblings of patients display a pattern of lateralization between that of probands and healthy controls, suggests observed abnormalities could have in part a genetic component.

It is interesting to note that there was significant behavioral impairment in the schizophrenia patients on the BET task but not the EToM. This is somewhat counterintuitive since the BET appears to be easier to perform, and controls are near ceiling, both of which would normally bias group differences in behavioral results in the opposite direction. A possible explanation for this finding is that the difficulty of the EToM task obscures differences between groups as controls and patients' siblings do not perform near ceiling, as is the case with BET. In fact, the present results are in agreement with previous data by our group and others, which have described ToM deficits in both first-degree relatives and patients for verbal tests, but not for visual tests as those probed herein. In this regard, it has been suggested that psychosis treatment may ameliorate social cognitive deficits in patients to levels comparable to those of their relatives, and even healthy controls (de Achával et al., 2010).

A series of limitations of the present study should be taken into account for precise interpretation of results. The relatively small size of the sample might have obscured significant relationships between patterns of brain activity and social competence, resulting in an incomplete description of such variables; moreover, some participants in the patients and relatives groups were actual siblings, thus making these samples not completely independent. Second, all participants were recruited at the same center and were homogeneous in culture, ethnicity, and geographical distribution, thus limiting the generalizability of results to all patients with schizophrenia. Third, all patients were treated with antipsychotics, and some of them also received antidepressants and sedative-hypnotic drugs, which might have affected their performance in tests and brain activation during fMRI scanning. However, this limitation does not apply to unaffected siblings of patients, who were free of medications. Fourth, being a cross-sectional, correlational study, the present results do not permit to infer causation between patterns of brain activation and social competence, which in addition may be affected independently by general cognitive abilities. However, most recent data suggest that variance in social functioning due to neurocognition is explained by the effects of the latter on social cognitive abilities (e.g., Green et al., 2012). Also, correlation between an index of brain activity lateralization during a social cognitive task and social competence, was evident only in

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patients with schizophrenia. This raises the possibility that the observation of right hemisphere structure activity related to social competence in healthy individuals does not reflect a brain lateralization phenomenon but simply local activity in areas relevant to social cognitive processing. Last, part of the evidence reviewed above on possible molecular mechanisms of brain lateralization development, suggests primate brain lateralization could be, in certain respects, gender-specific, as evidenced by the homology of X- and Y-linked protocadherins (PCDHX and PCDHY, respectively), which are involved in the development of brain lateralization (see McGlone, 1977; Jazin and Cahill, 2010; Priddle and Crow, 2013). It is possible that intergroup differences be partly due to a different gender composition. The present study is not adequately powered to explore this possibility, but again this is not applicable to differences seen between patients' siblings and healthy controls, which had an identical sex composition.

If confirmed in other samples of patients, the relationship between brain activity during social cognitive tests and social competence described herein warrants its consideration as a potential neurobiological indication of risk for schizophrenia. These results also add to accumulating evidence that social deficits in schizophrenia may reflect abnormal functioning of right-hemisphere structures involved in the processing of social cognitive information. If such functional abnormalities ultimately rest upon structural right-hemisphere deficits is an open question subject to further study.

Role of the funding source

Agencia de Promoción, University of Buenos Aires, CONICET, and FLENI had no role in the design of the experiments and the preparation of the manuscript.

Contributors

MFV, DDA, CBN, and SMG designed the study. MFV, DDA, LD, MGG, MNC, EYC, and SMG conducted the experiments and analyzed the data. MFV and SMG wrote the first version of the manuscript. All authors discussed the results and contributed to the final version of the manuscript.

Conflict of interest

CBN is a consultant to Xhale and Takeda, is a stockholder of CeNeRx BioPharma, NovaDel Pharma, Inc., PharmaNeuroBoost, Revaax Pharma, and Xhale, he is the owner of patents for method and devices for transdermal delivery of lithium (US 6,375,990B1) and method of assessing antidepressant drug therapy via transport inhibition of monoamine neurotransmitters by ex vivo assay (US 7,148,027B2), he is in the board of directors of AFSP, NovaDel Pharma, Inc., and is in the scientific advisory board of American Foundation for Suicide Prevention (AFSP), CeNeRx BioPharma, National Alliance for Research on Schizophrenia and Depression (NARSAD), NovaDel Pharma, Inc., PharmaNeuroBoost, Anxiety Disorders Association of America (ADAA). All other authors report no conflicts of interest.

Acknowledgments

Funding was provided by the Agencia de Promoción, Ministerio de Ciencia y Tecnología of the Argentine Government (PICT-2007-01643), University of Buenos Aires (UBACyT 2011-2014, School of Psychology), CONICET (PIP 2012-2015) and FLENI Dept. of Teaching and Research supported this work. SDG. LJD, DdA and MNC are doctoral research fellows from CONICET.

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