Psychiatry Research: Neuroimaging ∎ (∎∎∎∎) ∎∎∎–∎∎∎

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

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

Cluster B personality symptoms in persons at genetic risk for schizophrenia are associated with social competence and activation of the right temporo-parietal junction during emotion processing

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ARTICLE INFO

Article history:
Received 8 January 2013
Received in revised form
24 September 2013
Accepted 25 October 2013

Keywords:
fMRI
Schizophrenia
Siblings
Personality
Cluster B
Temporo parietal junction

ABSTRACT

Personality disorders are common in nonpsychotic siblings of patients with schizophrenia, and some personality traits in this group may be associated with an increased risk for full-blown psychosis. We sought to establish if faulty right-hemisphere activation induced by social cognitive tasks, as previously described in patients with schizophrenia, is associated with specific personality symptoms in their unaffected siblings. We observed that cluster B personality symptoms in this group were inversely related to activation in the right temporo parietal junction (rTPJ, a structure critical in social cognitive processing) in response to a basic emotion processing task and also to social competence, whereas in contrast to our initial hypothesis, cluster A traits were not associated with right hemisphere activation during emotion processing or with social competence. These findings suggest the existence of clinical traits in at-risk individuals which share a common neurobiological substrate with schizophrenia, in regards to social performance.

1. Introduction

Early epidemiological work on schizophrenia demonstrated that close biological relatives of patients display higher than expected rates of "subsyndromal" disease, in part, in the form of personality disorders (Kety et al., 1971, 1994). This has been confirmed in more recent samples, which found an excess of cluster A personality traits in close relatives of psychotic patients (Braff, 1981; Dickey et al., 1999; Kendler et al., 1993). The presence of other personality traits, particularly cluster B, has also been described (Hogg et al., 1990; Lysaker et al., 2004; Schultze-Lutter et al., 2012). Cluster A traits result in an "odd" or "eccentric" personality pattern, including suspiciousness, eccentric thinking, or even peculiar perceptual experiences, whereas cluster B traits are significant for "dramatic" manifestations such as attention-seeking behavior, deceitfulness, impulsitivy and even self-directed aggression (American Psychiatric Association, 2000; Kendler et al., 2008). In fact, some data suggest that genetic risk for personality traits do not necessarily overlap with DSM-IV categories, thus suggesting that genetic risk for schizophrenia may in turn result in diverse personality traits (Kendler et al., 2008). In the last decade, several groups have attempted to define prodromal traits predictive of future conversion to schizophrenia in at-risk subjects, especially after demonstration that early intervention shortening the duration of active symptoms improves the ominous prognosis of schizophrenia (Klosterkotter et al., 2011). Most efforts in this direction have involved either the definition of early or subsyndromal positive manifestations of psychosis, or neuropsychological deficits (Klosterkotter et al., 2011; Stanford et al., 2011). However, the predictive ability of these manifestations has been relatively modest even in large samples, ranging between 13% and 50% for transition to a psychotic episode, and with substantial variance even in the same center. Ideally, putative clinical and neuropsychological predictors could be complemented with neurobiological predictors,

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http://dx.doi.org/10.1016/j.pscychresns.2013.10.008

as exemplified by the model predicting conversion from amnestic mild cognitive impairment to Alzheimer's dementia (Westman et al., 2012).

We recently described a specific failure in activation of right-hemisphere structures concerned with social cognition in patients with schizophrenia and their nonpsychotic siblings (de Achaval et al., 2012). In the present study we sought to establish if specific personality traits in that sample are associated with brain activation abnormalities characteristic of the full-blown syndrome. Available studies describe cluster A personality disorders and traits as clinically and biologically similar to schizophrenia (e.g., Tarbox and Pogue-Geile, 2011). In addition, recent work suggests that cluster A-schizoid traits in patients at risk for psychosis are significant predictors of conversion, thus underscoring the relationship this symptom dimension exhibits with full-blown psychosis (Schultze-Lutter et al., 2012). This personality trait dimension involves persistent deficits in social functioning akin to those seen in schizophrenia. This led us to the hypothesis that cluster A traits account for shared neurobiological alterations underlying social deficits, between siblings discordant for schizophrenia, as previously demonstrated (de Achaval et al., 2012). In the present study, we sought to establish if specific personality traits in the nonpsychotic siblings of schizophrenia patients in that sample are associated with brain activation abnormalities characteristic of the full-blown syndrome. We predicted that cluster A traits would be associated with both a deficit in social functioning and a failure to recruit right-hemisphere structures concerned with social cognition (i.e., inferior frontal gyrus, and superior temporal sulcus/temporoparietal junction).

Based upon previous data, we explored the relationship between brain activation during social cognitive tasks and personality traits in three areas, namely the temporoparietal junction (TPJ), and the inferior (IFG) and middle (MFG) frontal gyri. Among these, different studies have assigned a critical role to the TPJ, especially on the right hemisphere, for the processing of social cognitive information, both verbal and nonverbal (Völlm et al., 2006; Decety and Lamm, 2007; Morishima et al., 2012; Santiesteban et al., 2012). Our group and others have recently described deficits in activation of the rTPJ in patients with schizophrenia, suggesting this is a finding characteristic of the disease (Das et al., 2012; de Achaval et al., 2012), and thus probably related to their deficits in social function. IFG and MFG have also been implicated in different aspects of emotion processing and empathy and theory of mind (Shamay and Tsoorg, 2011; Bereczkei et al., 2013), along with structural alterations in schizophrenia (Kikinis et al., 2010; Yang et al., 2010), and displayed deficits of activation in the right hemisphere in a previous study (de Achaval et al., 2012).

On the basis of these observations, we predicted that cluster A traits would be associated with a failure to recruit right-hemisphere structures concerned with social cognition (i.e., inferior frontal gyrus, superior temporal sulcus/temporoparietal junction). Moreover, we expected that such neural activity abnormalities would be related to actual social competence deficits in persons who are at heightened genetic risk for schizophrenia. To test these hypotheses, we employed a functional magnetic resonance imaging (fMRI) paradigm of identification of basic emotions in faces, and a recently developed test of social competence in schizophrenia, the test of adaptive behavior in schizophrenia (TABS) (Velligan et al., 2007).

2. Methods

This was a cross-sectional study on the relationship between personality traits, deficits on brain activation, and social competence in unaffected siblings of patients with schizophrenia. We recently reported on the effects of different social cognitive tasks in brain activation in this sample (de Achaval et al., 2012). Here we sought to determine if abnormalities shared by siblings discordant for schizophrenia are related, in the nonpsychotic siblings, to specific personality traits.

2.1. Subjects

Two psychiatrists (SMG, EYC) and a psychologist (DDA) assessed all participants, who were evaluated at the Cognitive Neurology Section and the Psychiatry Department at FLENI Hospital, Buenos Aires, Argentina. All participants were right-handed (as determined clinically by use of right extremities in two motor activities other than handwriting, and no report of preference for left extremities), and provided written informed consent as approved by the local bioethics committee, and therefore performed in accordance with the ethical standards set by the 1964 Declaration of Helsinki. Details of the sample of participants were given elsewhere (de Achaval et al., 2012) and are summarized in Table 1.

Fourteen unaffected siblings of patients with schizophrenia (6 females and 8 males, 30.4 ± 4.8 years of age) admitted at FLENI Departments of Neurology and Psychiatry, were recruited. Participants had 15.1 ± 2.4 years of formal education; parental years of education were 12.8 ± 3.3. 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) a medication history of antipsychotics, antidepressants, or mood stabilizers. In addition, history of head trauma involving loss of consciousness, and major neurological disorders potentially affecting results, including Parkinson's disease, alcohol dependence, and diabetes, were ruled out in a semi structured clinical interview designed for use in this protocol, and including a checklist for the aforementioned exclusion criteria, with the participant and a first-degree relative. Given the reported increased prevalence of nonpsychotic psychiatric disorders in first-degree relatives of schizophrenia patients, we planned to exclude siblings with syndromes warranting psychopharmacological treatment, so as to avoid that significant depressive or anxiety symptoms interfere with the results. No potential participants were excluded per this criterion, and anxiety and depressive symptoms were not higher in siblings of schizophrenia patients as compared to control participants (de Achaval et al., 2012).

Data on brain activation and social competence in a sample of 14 healthy volunteers and a sample of 14 patients with schizophrenia were also collected for comparison (de Achaval et al., 2012). The gender composition of healthy individuals was identical to that of the siblings (6 females, 8 males), and there were no significant differences in age (28.4 ± 8.3 years), years of education ($15.2. \pm 1.8$), or years of parental education (14.4 ± 3.6). Healthy comparison individuals were recruited from the local community; 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 psychiatrist (EYC) and (b) a medication history of antidepressants, antipsychotics, or mood stabilizers. Patients with schizophrenia (1 female, 13 males) were also comparable in age (30.6 ± 7), years of education (14 ± 2), and years of parental education (11.2 ± 3.6) (de Achaval et al., 2012). Patients were recruited if they (a) had a DSM-IV-TR diagnosis of schizophrenia, any subtype, confirmed with a composite international diagnostic interview (Robins et al., 1988) administered by a consultant psychiatrist (EYC), (b) were aged 18 to 50 years, and (c) had been on the same medications for at least two weeks. Patients reported having been on antipsychoticmedications during the whole disease process, i.e., eight years on average (Table 1), but this could not be confirmed with chart review, nor were data available on exposure to typical vs. atypical antipsychotics during that period. Exclusion criteria were (a) misuse or addiction to illegal substances in the previous 6 months, (b) active symptoms having recently (two weeks) warranted antipsychotic dose adjustment or admission to the hospital, day hospital, or intensive outpatient treatment, or (c) a history of mental retardation.

2.2. Behavioral measures

Previous to fMRI studies, all participants were evaluated with the mini mental state examination (MMSE, Folstein et al., 1975), and the MATRICS consensus cognitive battery (Kern et al., 2008; Nuechterlein et al., 2008). MMSE was used as a screening test before participants underwent further testing. They were also tested for premorbid intelligence with the word accentuation test (WAT, Del Ser et al., 1997), and with the facial recognition test (FRT, Benton and Van Allen, 1968) to ensure participants did not have nonspecific deficits in facial recognition, which could have interfered with the test results; all participants had $>80\%$ accuracy in this test (Table 1).

Personality traits were measured with a semi-structured interview based upon the SCID-II questionnaire (First, 1997) and social functioning was assessed with the test of adaptive behavior in schizophrenia (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 is comprised of 6 test areas including medication management (the person is asked to fill a medication container based upon instructions from the doctors and to remember to call for a new prescription at a specific time), empty bathroom (the person is asked what would be needed to stock an empty bathroom to use to get ready everyday), shopping skills (the person is asked how they would

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Table 1
Demographic data, personality, cognitive performance, and emotional performance.

	Patients ($n=14$)	Siblings ($n=14$)	Controls ($n=14$)	Overall p	P-C p	P-S p	S-C p
Age (years)	30.6 ± 7	30.4 ± 4.8	28.4 ± 8.3	0.062	0.654	0.996	0.705
Education (years)	14 ± 2	15.1 ± 2.4	15.2 ± 1.8	0.234	0.280	0.323	0.995
Parental education (years)	11.2 ± 3.6	12.8 ± 3.3	14.4 ± 3.6	0.071	0.068	0.447	0.536
Women, *n* (%)	1 (7)	6 (43)	6 (43)	0.357			
Age at onset (years)	23.5 ± 4.8						
Disease duration (years)	7.8 ± 4.5						
MMSE score	28.8 ± 1.5	28.9 ± 1.4	29.5 ± 0.9	0.276	0.311	0.988	0.386
WAT score	32.4 ± 4.3	33.1 ± 5.6	34.6 ± 7.9	0.638	0.626	0.958	0.793
TABS	16.8 ± 2.4	20.0 ± 2.8	19.3 ± 7.9	0.247	0.409	0.258	0.940
SCID II							
Cluster A		4.0 ± 3.78					
Cluster B		10.21 ± 7.15					
Cluster C		5.5 ± 4.22					
General score		19.71 ± 13.85					
***MCCB* (*percentile*)**							
Speed of processing	4 ± 10[a,b]	29 ± 26[a]	47 ± 18	< 0.001	< 0.001*	0.004*	0.038*
Attention/vigilance	17 ± 21[a]	27 ± 30[a]	53 ± 22	0.001	0.001*	0.545	0.023*
Working memory	17 ± 19[a]	38 ± 33	58 ± 26	0.001	0.001*	0.115	0.108
Verbal learning	23 ± 22[a]	32 ± 30[a]	59 ± 24	0.002	0.002*	0.584	0.026*
Visual learning	28 ± 29[a]	51 ± 41	65 ± 23	0.014	0.011*	0.158	0.471
Reasoning/problem solving	24 ± 22[a]	29 ± 29[a]	49 ± 31	0.002	0.002*	0.501	0.039*
Social cognition	21 ± 27[a]	32 ± 32[a]	63 ± 26	0.001	0.001*	0.531	0.019*
BET							
***Response latency* (*s*)**							
Experimental condition	2.41 ± 0.48[a]	2.18 ± 0.46	1.88 ± 0.44	0.014	0.010*	0.373	0.210
Control condition	1.89 ± 0.53[a]	1.60 ± 0.40	1.35 ± 0.34	0.009	0.006*	0.200	0.287
***Response accuracy* (%)**							
Experimental condition	95 ± 4[a]	97 ± 5	99 ± 2	0.043	0.033*	0.354	0.449
Control condition	98 ± 3	98 ± 5	99 ± 2	0.777	0.933	0.932	0.758
FRT	22.7 ± 2.6	24.6 ± 1.7	23.1 ± 4.9	0.294	0.940	0.296	0.474

MMSE: mini-mental state exam; WAT: word accentuation test; TABS: test of adaptive behavior in schizophrenia; MCCB: MATRICS consensus cognitive battery; SCID II: structured clinical interview for DSM-IV axis II personality disorders; BET: basic emotions task; FRT: face recognition test.
Shown are mean ± standard deviation or number (%) of cases.
ANOVA followed by Tukey's HSD post hoc was used for all variables except gender (Chi-Square). Overall p: Overall ANOVA (or Chi-Square); P-C *p*, P-S *p* and S-C *p*: post-hoc (Tukey's) pairwise comparison for patiens versus controls (P-C), patients versus siblings (P-S) and siblings versus controls (S-C).

* Statistically significant (adjusted $p < 0.05$) difference in pairwise comparison.
[a] Significantly different from healthy controls.
[b] Significantly different from siblings.

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 for each subtest and the total score reflect the percent correct. Higher scores indicate better adaptive functioning. In addition, based on SCID-II results, two siblings of patients fulfilled DSM-IV-TR criteria for schizoid personality disorder.

2.3. fMRI paradigm

The paradigm for probing brain activation induced by social cognitive tasks has been described in detail elsewhere (de Achaval et al., 2012). Briefly, we used the Picture of Facial Affect (Ekman and Friesen, 1976) to ascertain activation induced by basic emotion processing. We used a block design ABAB paradigm for the task, which consisted in 14 blocks of 25 s; half of them were an experimental condition (i.e. emotion processing) and the other half a control condition. In the experimental condition, a series of 4 photographs of faces and two of the six words naming basic emotions were simultaneously presented to the subjects (e.g., happy-sad), and they were asked to press a button to indicate which of the two words best described the mental state of the person in the photograph. A single device with two buttons operated with the right hand was used in the experiment. In the control condition, 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 (male–female). 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 counter-balanced to left and right side of the screen. All the stimuli and responses were administrated with the Presentation software (Neurobehavioral Systems, Inc., Albany, CA, USA). Fig. 1 shows an example of one presentation in each condition.

2.4. fMRI data acquisition

Magnetic resonance imaging (MRI) data were acquired on a 3 T GE Hdx scanner with an 8 channel head coil. Change in blood-oxygenation-level-dependent (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). Also a structural MRI was acquired for every subject 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). One session of 155 volumes was taken per subject.

2.5. Data analysis

2.5.1. 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 $p < 0.05$. All tests were performed with the SPSS version 13.0 software (SPSS Inc.).

2.5.2. fMRI analysis

2.5.2.1. 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 using the Montreal Neurological Institute reference brain (Ashburner

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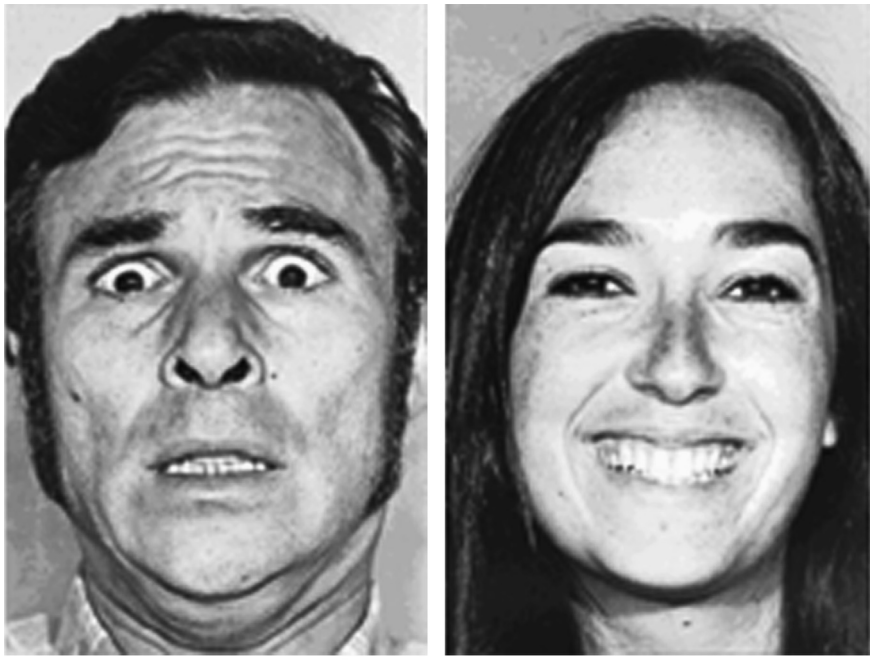

Fig. 1. Example of stimuli used for assessment of basic emotion processing. During control tasks, the same stimuli were used but the participant was asked to decide the gender of the depicted person.

and Friston, 1999). 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).

2.5.2.2. Statistical analysis. Individual analysis was computed using the general linear model including the control (gender) and experimental (emotion) conditions using a boxcar model convolved with the canonical hemodynamic response function. Then, as we wanted to analyze the explicit emotion processing, a linear contrast EMOTION–GENDER (E–G) was applied to the individual designs.

The mean percent signal change of the beta values from the individual contrast E–G was obtained from three pairs of regions of interest (ROIs): (1) the left inferior frontal gyrus (IFG) defined as a sphere centered at (−45, 18, 2), and the right IFG centered at (40, 24, 2); (2) the left middle frontal gyrus (MFG) at (−48, 15, 26) and the right MFG at (48, 15, 26) and (3) the left superior temporal gyrus (STG) at (−51, −45, 3) and the right STG at (51, −45, 3). All ROIs were spheres of 10 mm radius built using MarsBar algorithm. The coordinates were selected from the random effect analysis made on controls, siblings and patients E–G contrasts, previous shown (de Achaval et al., 2012).

The mean percent signal change for each ROI and subject was entered into a Spearman's Rho correlation test to explore the relationship between brain activation at each ROI and SCID-II score in the clusters A–C. We also explored the relationship between TABS and SCIID-II scores. A Bonferroni–Holm correction for multiple comparisons was used to correct significance of Spearman's Rho independently for each pair of bilateral ROIs when correlating activation with scores on each of the three SCID-II personality clusters (2 ROIs × 3 Personality Clusters). Significant correlations were assumed at $p < 0.05$. All reported results are two-tailed. Statistical Package for the Social Sciences (SPSS version 13, SPSS Inc., Delaware, USA) was used for analyses.

Additionally, three independent regression analyses were done between the E–G contrast in the whole brain and the SCIID-II scores for each cluster, resulting in a single brain map for each regression, and showing the brain areas that are modulated by the personality traits ($p < 0.001$, uncorrected; SPM5, Wellcome Department of Cognitive Neurology, London, UK, implemented in MATLAB 7 (Mathworks Inc., Sherborn, MA, USA).

3. Results

3.1. Demographic, clinical, and performance data

Table 1 summarizes demographic characteristics, cognitive function, and performance in the scanner of siblings discordant for schizophrenia and comparable healthy controls, as described previously (de Achaval et al., 2012). Briefly, nonpsychotic siblings were comparable to healthy individuals in all demographic characteristics and intelligence as assessed by the WAT test, but a detailed evaluation of cognitive functioning with MATRICS consensus cognitive battery revealed deficits in some dimensions (Table 1), making this sample of siblings discordant for schizophrenia similar in this regard, and different from comparable healthy controls, as described previously (de Achaval et al., 2012). Performance in the scanner, in terms of accuracy and latency of responses, was similar in nonpsychotic siblings and healthy controls (Table 1).

3.2. Correlation analyses

Fig. 2a shows the relationship between activation in the rTPJ during basic emotion recognition, and severity of cluster B (green circles) or A (blank squares) personality symptoms. Table 2 shows the correlation matrix for ROIs and SCID II clusters. Only the correlation with cluster B traits achieved statistical significance (Table 2, Fig. 2a). Mean extracted ROI signal in the E–G contrast for comparable healthy individuals (blue square), patients with schizophrenia (red diamond) and siblings (green circles) are also shown in Fig. 2. Cluster C traits were unrelated to activation in the rTPJ (not shown). No correlations were found for SCID-II scores and activation of either IFG or MFG, or left TPJ (not shown).

Fig. 2b shows cluster A (blank squares) and B (green circles) traits in nonpsychotic siblings of patients with schizophrenia in relation to social competence as measured by the TABS score (Fig. 2b). Only cluster B traits achieved significance when correcting for multiple comparisons (Table 2). The distribution of values for nonpsychotic siblings was located between healthy individuals (who displayed maximum performance, blue square, and patients, red diamond). Cluster C traits were unrelated to social functioning in the present sample of nonpsychotic siblings of patients with schizophrenia (not shown).

Fig. 3 shows the regression analysis between whole brain activity and cluster B symptomatology. The main area of correlation

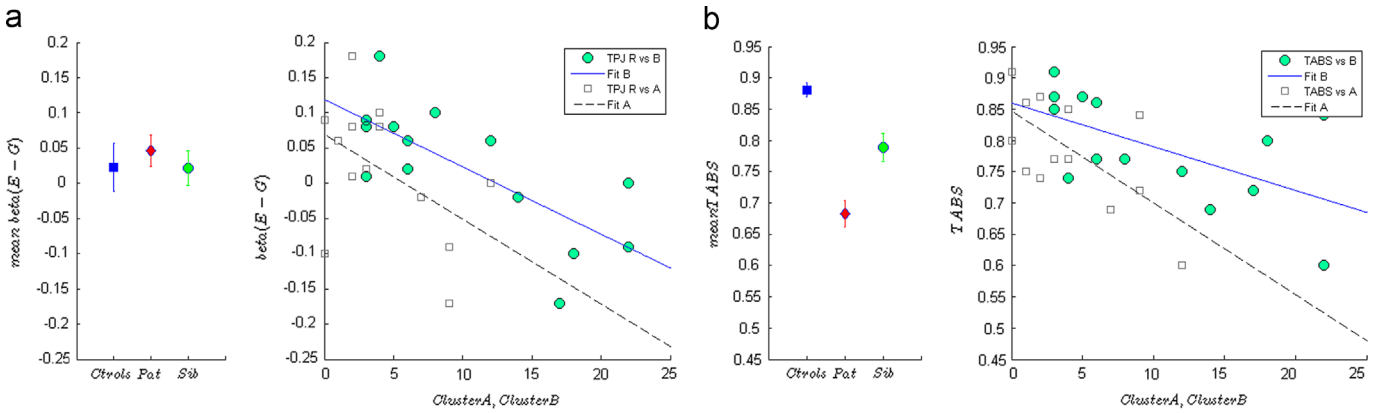

Fig. 2. Correlation between cluster A (blank squares, dashed line) or cluster B (green circles, solid line) symptomatology and activity in the rTPJ during a basic emotion processing task (a) and social competence (b) in nonpsychotic siblings of patients with schizophrenia. Cluster B symptomatology is associated with lower activation at the level of the rTPJ and decreased social competence. Brain activation and social competence in nonpsychotic siblings are located between mean values (± standard error) for comparable healthy persons (blue) and psychotic siblings (red). G: gender (control) condition; E: Emotion (experimental) condition. Please see the text for details. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 2
Correlation between SCID-II Scores, TABS and ROIs.

	Mean	Std. Error	Cluster A	Cluster B	Cluster C
IFG L	0.09	0.05	−0.492	−0.298	0.048
			0.444	0.900	1
IFG R	0.03	0.04	−0.381	−0.394	−0.065
			0.820	0.820	1
MFG L	0.15	0.04	−0.368	−0.173	−0.191
			0.975	1	1
MFG R	0.07	0.05	−0.272	−0.468	−0.272
			1	0.546	1
STG L	0.05	0.03	−0.169	−0.235	−0.211
			1	1	1
STG R	0.02	0.02	−0.359	−0.700*	−0.537
			0.832	0.030*	0.240
TABS	69.86	7.33	−0.577	−0.626	−0.279
			0.062	0.051*	0.334

SCID II: Structured Clinical Interview for DSM-IV Axis II Personality Disorders; TABS: Test of Adaptive Behavior in Schizophrenia; ROIs: regions of interest; IFG: inferior frontal gyrus; MFG: middle frontal gyrus; STG: superior temporal gyrus; L: left hemisphere; R: right hemisphere. For each correlation, Spearman's Rho (top) and Boferroni–Holm corrected *p* value (bottom) are shown.

* Significant correlations are marked with a.

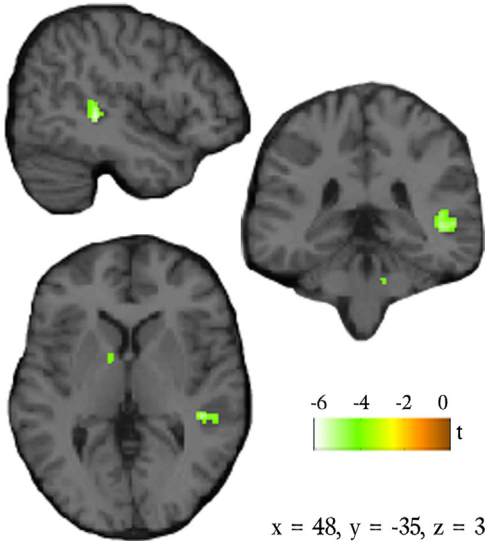

Fig. 3. Regression analysis between whole brain activation during the emotion processing relative to control tasks and personality traits. Figure shows the areas whose activity correlated inversely with cluster B. Clusters A or C scores were not significantly correlated with brain activity during the explicit emotion processing task. Please see the text for details.

involved the rTPJ. No areas were correlated with clusters A or C symptoms (not shown).

4. Discussion

The main finding of this study is that the presence of cluster B, but not cluster A, personality traits in nonpsychotic siblings of schizophrenia patients, is associated with degree of activation of the rTPJ in an emotion processing task, and with social competence as evaluated by the TABS.

Social cognition is a complex construct that encompasses the different processes involved in the interaction between human beings (Adolphs, 1999). Emotion processing, the ability to perceive and using emotion, is the construct used in this study, and a basic step in social cognitive abilities, as assessing another person's intentions (usually referred to as theory of mind, Premack and Woodruff, 1978) requires an intact capacity for appraisal of the person's emotional status and one's own response to it (Ochsner 2009; de Achaval et al., 2010). From a neurobiological perspective, it has been repeatedly documented that rTPJ activation is critical for the normal performance of different social cognitive skills (Gallagher and Frith, 2003; Saxe and Kanwisher, 2003). The present study provides preliminary evidence for a relationship between the presence of cluster B personality traits in persons at increased risk for schizophrenia and deficits in rTPJ activation during a social cognitive task. If replicated, this finding may lead to further studies that explore the commonalities in the neurobiology between cluster B personality traits and syndromal schizophrenia. Social cognitive deficits have been recently shown to be the best predictors of conversion to schizophrenia in at-risk subjects (Cannon et al., 2008; Niemi et al., 2003). If faulty activation of right hemispheric structures involved in social cognition is also associated with increased risk in persons with a genetic predisposition remains open to further investigation (Mitchell and Crow, 2005). In this regard, the fact that in this sample cluster B traits were related to degree of deficit in actual social competence, in our view supports the possibility that brain activation deficits determine social deficits in persons at risk for schizophrenia. While causation cannot be readily inferred in a cross sectional study for the relationship between functional brain alterations, clinical traits, and social deficits, the present results raise the possibility

these variables reflect different aspects of a common phenomenon. This is open to further investigation, including longitudinal observational studies on conversion to psychosis in at-risk subjects.

If confirmed in samples of at-risk individuals in whom liability to develop full-blown psychosis has been assessed with appropriate instruments (including BLIPS and APS, Schimmelmann et al., 2013), our results might have a bearing on the definition of the prodromal phase of schizophrenia and identification of susceptible at-risk individuals, complementing clinical symptoms, on the basis of shared pathophysiological traits with fully developed psychosis. Most efforts have involved the development of scoring systems based upon clinical characteristics, either cross-sectional, historical (e.g., obstetrical complications), or familial (i.e., presence of close relatives who suffer schizophrenia). These efforts have yielded relatively modest results, namely 12-month rates of transition to first-episode psychosis ranging between 13% and 50% (Klosterkotter et al., 2011). Given that the annual incidence of psychosis of any type in the general population is about 0.04%, such conversion rates are still significant. Ideally, however, these clinical predictors would be augmented, for more accurate risk definition, by biomarkers, much as has been demonstrated in Alzheimer`s disease, where neuroimaging and biochemical variables dramatically increase the predictive capacity of conversion from mild cognitive impairment, to Alzheimer's disease (e.g., Westman et al., 2012). The present results therefore offer a heuristically valid hypothesis linking clinical traits (i.e., cluster B symptoms), actual social dysfunction, and a deficit in activation of the rTPJ, widely implicated in social cognitive abilities in normal conditions (Saxe and Kanwisher, 2003). Whereas as previously stated the sample may have lacked power to detect an underlying neurobiological abnormality associated to cluster A symptoms, according to our initial hypothesis, the possibility exists that distinct neurobiological dysfunction patterns ultimately lead to both clinical traits and social dysfunction in persons at heightened genetic risk for schizophrenia. This observation notwithstanding, the present findings do not readily support one of the primary hypothesis of the study—namely, that there exists a specificity of brain functional alterations underlying social cognitive deficits for cluster A personality traits, considered – on the basis of epidemiological studies – to be in the middle of the clinical continuum from normalcy to full-blown psychosis (Braff, 1981; Dickey et al., 1999; Kendler et al., 1993). However, there is previous evidence to suggest that cluster B traits are preferentially associated with conversion to psychosis in predisposed subjects as compared to cluster A traits (Hogg et al., 1990; Lysaker et al., 2004; Schultze-Lutter et al., 2012). In fact, the inception of the term "borderline" to designate diverse prominent features of cluster B personality, follows early observations that the syndrome was different from neuroses and hypothesized to be related, in its manifestations, to schizophrenia (Stern, 1938).

The present study was limited by the relatively small number of participants (thus increasing the chance of false positives), the homogeneity of the sample in regards to geography, ethnicity, and cultural background, and the fact SCID-II was the only instrument to measure personality traits; in this regard, a specific personality rating scale would have permitted a better appraisal of the relationship between brain activation patterns and clinical personality traits, even though SCID-II scores have been usually shown to correlate well with such instruments, and have been related to brain imaging variables in other populations (e.g., de Araújo Filho et al., 2009; Simonsen and Simonsen, 2009). Moreover, the results in the three clusters might differ due to a greater variance originated in different amounts of questions in the SCID-II. Also, this study did not use clinical scales for assessment of high risk subjects (Schimmelmann et al., 2013), which would have permitted a better definition of the role of brain activity patterns described herein. In addition, the observed correlation between the presence of cluster B traits and rTPJ activation during an emotion processing task could also be characteristic of cluster B personality disorders, and unrelated to schizophrenia. Since we did not include a sample of personality disorder patients, we cannot rule out this possibility. An additional comment is in order regarding the fact that, in the present study, we did not observe a distinct activation of areas traditionally associated with facial emotion processing, including amygdala and fusiform gyrus (e.g., Bajaj et al., 2013). A possible explanation for this finding is that such areas are usually associated with implicit emotion processing, which was probably cancelled out in the present study by the fact the control tasks involved the same faces as the experimental tasks, as the experimental paradigm used herein involved the naming of emotions, i.e., an explicit task. Last, siblings of schizophrenia patients displayed a number of cognitive functioning differences with healthy subjects, which could have also influenced their performance.

Future studies should address two important questions. First, if persons at heightened genetic risk for schizophrenia who also display abnormal activation of rTPJ during social cognitive tasks convert to full psychosis more frequently. Second, if cluster B traits are related per se to faulty involvement of right-hemisphere structures even in persons without increased risk for schizophrenia, e.g., patients with borderline personality disorder. Whether the present results have a bearing on the definition of neurobiological signatures of schizophrenia in at-risk individuals which therefore improve the prediction of full-blown psychosis, is a question open to definition by further studies employing longitudinal observation methods.

Acknowledgments

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), and FLENI Dept. of Teaching and Research supported this work. SDG. DdA and MNC are doctoral research fellows from CONICET. 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 conflict of interest. MCG, MFV, DdA, JC, CBN, and SMG designed the study. MCG, MFV, DdA, EYC, MNC, JP, and SMG run the experiments and analyzed the data. MCG, MFV, and SMG wrote the first version of the manuscript. All authors contributed to and approved the final version of the manuscript. We thank Ms. Sofía Abrevaya for her technical help with processing of MATRICS and TABS data.

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Please cite this article as: Goldschmidt, M.G., et al., Cluster B personality symptoms in persons at genetic risk for schizophrenia are associated with social competence and.... Psychiatry Research: Neuroimaging (2013), http://dx.doi.org/10.1016/j.pscychresns.2013.10.008