Psychiatry Research: Neuroimaging 221 (2014) 30–36

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
Available online 31 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