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

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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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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