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Association of familial risk for schizophrenia with thalamic and medial prefrontal functional connectivity during attentional control

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ABSTRACT

Anomalies in behavioral correlates of attentional processing and related brain activity are crucial correlates of schizophrenia and associated with familial risk for this brain disorder. However, it is not clear how brain functional connectivity during attentional processes is key for schizophrenia and linked with trait vs. state related variables. To address this issue, we investigated patterns of functional connections during attentional control in healthy siblings of patients with schizophrenia, who share with probands genetic features but not variables related to the state of the disorder. 356 controls, 55 patients with schizophrenia on stable treatment with antipsychotics and 40 healthy siblings of patients with this brain disorder underwent the Variable Attentional Control (VAC) task during fMRI. Independent Component Analysis (ICA) is allowed to identify independent components (IC) of BOLD signal recorded during task performance. Results indicated reduced connectivity strength in patients with schizophrenia as well as in their healthy siblings in left thalamus within an attentional control component and greater connectivity in right medial prefrontal cortex (PFC) within the so-called Default Mode Network (DMN) compared to healthy individuals. These results suggest a relationship between familial risk for schizophrenia and brain functional networks during attentional control, such that this biological phenotype may be considered a useful intermediate phenotype in order to link genes effects to aspects of the pathophysiology of this brain disorder.

1. Introduction

It is well known that risk for schizophrenia is mostly explained by genetic factors (Gottesman et al., 1987). However, the heterogeneity of the clinical phenotype and state-related variables make it difficult to identify pathophysiological mechanisms associated with genetic risk. Healthy siblings of schizophrenia patients share half of the genetic variation with probands on average, have increased risk for the disorder, and are not affected by variables related to the state of the illness. Thus, investigation of these individuals may allow for identification of the biological correlates implicated in schizophrenia and more easily linked with gene effects (Bertolino and Blasi, 2009).

Several studies have demonstrated that anomalies in attentional processes are key for schizophrenia (Kahn and Keefe, 2013; Weickert et al., 2000) and are also present in healthy siblings of patients (Egan et al., 2000; Toulopoulou et al., 2010). Patients with schizophrenia and their healthy relatives have an abnormal response of brain nodes during cognitive tasks involving attentional processing in both cortical and sub-cortical areas (Delawalla et al., 2008; Gur et al., 2007; MacDonald et al., 2009; Pergola et al., 2015; Smieskova et al., 2013). In particular, Blasi et al. (2010) revealed that prefrontal activity is altered in patients with schizophrenia during attentional control, a cognitive process providing a top-down bias that allows flexible allocation of attentional resources to relevant stimuli while suppressing those that are less relevant (Blasi et al., 2007; Desimone and Duncan, 1995).

A growing body of evidence supports the notion that dysfunctional patterns of functional brain connectivity may be a crucial correlate of schizophrenia. Previous findings indicate lower prefrontal or thalamic connectivity during cognitive processing in patients with schizophrenia and in subjects with genetic liability for this disorder (Dauvermann

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et al., 2013; Pettersson-Yeo et al., 2011; Wagner et al., 2013, 2015; Whitfield-Gabrieli et al., 2009), although evidence of increased prefrontal connectivity has also been found (Whalley et al., 2005). However, to our knowledge, only one recent investigation has explored the relationship between genetic liability for schizophrenia and brain connections during components of top-down modulation of attention using Independent Component Analysis (ICA) (Poppe et al., 2015). The authors hypothesized that connectivity would be altered in the middle frontal gyrus and found evidence that familial risk for schizophrenia modulates a right fronto-parietal network that includes this brain region during context processing.

Importantly, anomalies of functional brain connectivity in schizophrenia have also been found in regions not directly involved in task performance, as suggested by studies focusing on the Default Mode Network (DMN) (Raichle et al., 2001; Smith et al., 2012), a set of brain areas including the medial prefrontal cortex (mPFC), the posterior cingulate cortex, the inferior parietal lobule, the precuneus, and the medial temporal lobe (Sambataro et al., 2013). Previous findings indicated increased DMN activity during rest and reduced activity during task performance (Fox et al., 2006). DMN activity is also anti-correlated with task-related areas (Fransson, 2005). It has been suggested that the DMN might subtend several brain processes, including self-reference (Gusnard et al., 2001) and introspection (Reiman and Caselli, 1999).

Several investigations have indicated abnormal DMN functional connections in patients with schizophrenia and in subjects with genetic liability for the disorder during rest in terms of either hyperconnectivity (Peeters et al., 2015; Tang et al., 2013) or attenuated connectivity strength (Chang et al., 2014; Khadka et al., 2013; Orliac et al., 2013). Other findings have indicated DMN hyperactivity (Whitfield-Gabrieli et al., 2009) or hypoconnectivity during task performance in both patients with schizophrenia and subjects with familial risk for the disorder (Garrity et al., 2007; Sambataro et al., 2010; Whalley et al., 2005). This is consistent with the view that abnormal DMN connectivity could lead to dysfunctions in the engagement of regions associated with cognitive processing (Fox et al., 2005).

Overall, the findings suggest that investigation of the relationship between patterns of brain functional connectivity and familial risk for schizophrenia is promising but still inconsistent, particularly when looking at the role of DMN during task performance. The reason for such discrepancy may lie in different factors, including patient characteristics, study design, and analysis strategies for imaging data. Furthermore, findings are scarce in regard to the domain of top-down modulation of attention, which is essential for schizophrenia, and there is a lack of investigations without a priori assumptions about target brain regions within functional networks.

The aim of this study is to use ICA (Calhoun et al., 2005, 2008) to investigate the association between familial risk for schizophrenia and functional connectivity in task-related brain regions and in the DMN during attentional control (Blasi et al., 2007). ICA allows for the measurement of functional connectivity by separating a multivariate signal into temporally coherent components (Calhoun et al., 2008). This tool is considered reliable for disentangling networks subserving different brain functions (Kim et al., 2009). We hypothesized that connectivity abnormalities in nodes subserving attentional control and in the DMN would be present in patients with schizophrenia and healthy siblings of patients with this disorder.

2. Materials and methods

2.1. Subjects and task

The experimental protocol was approved by the local ethical committee. All subjects were given a complete description of the study and its procedures. Written informed consent was obtained only after full comprehension of the protocol. The subjects enrolled in this study included 356 healthy individuals, 55 patients with schizophrenia on stable antipsychotic treatment for at least one month, and 40 healthy siblings of patients with the disorder (Table 1). Investigation of healthy siblings allowed us to address the association of the imaging phenotypes of interest in this study and familial risk for schizophrenia.

The siblings included in the present study were recruited while their affected relatives were hospitalized in the inpatient psychiatric unit at the Bari University Hospital. All these individuals gave written informed consent to the study and did not present any of the exclusion criteria described below. Four out of the forty healthy siblings were relatives of the patients enrolled in the study. Patients with schizophrenia who were relatives of the siblings here investigated and who were not included in the study were not eligible because of pharmacological instability, unavailability to undergo fMRI procedures or because of the presence of any of the exclusion criteria specified below. All healthy siblings enrolled in the study had only one sibling with diagnosis of schizophrenia. No other first-degree relatives of these healthy siblings were schizophrenia patients. In the sample of patients with schizophrenia, three out of the fifty-five subjects had another affected sibling. Such three affected siblings were not part of the sample of the present study. No other first-degree relative of the patients enrolled in this study was affected by schizophrenia.

Diagnosis of schizophrenia or exclusion of any psychiatric diagnosis was assessed with the Structured Clinical Interview for DSM-IV (First et al., 1996), handedness with the Edinburgh Inventory (Oldfield, 1971), and the pre-morbid intelligence quotient (IQ) using the Italian version of the revised Wide Reading Achievement Test - revised (Sartori et al., 1997). The patients, siblings and healthy controls had no history of drug or alcohol abuse within the last 6 months, head trauma with loss of consciousness, or any clinically significant medical condition.

All subjects underwent fMRI while performing the Variable Attentional Control (VAC) task, which requires three increasing levels of attentional control. This task has been used in several previous studies (Blasi et al., 2007, 2010, 2013a, 2013b; see Supplementary material).

2.2. Analysis of demographics and behavioral data

Analysis of co-variance (ANCOVA) and $\chi 2$ tests were used to compare demographics and behavioral data from the VAC task (percentage of correct responses and reaction time) as needed. Fisher's test was used for post-hoc analyses.

2.3. BOLD fMRI data acquisition and analysis

BOLD fMRI was performed on a GE Signa 3T scanner while subjects performed the VAC. The first level BOLD fMRI data analysis was performed with SPM8 (www.fil.ion.ucl.ac.uk/spm/) using standard procedures (see Supplementary material). Then, one group spatial ICA was performed using the infomax algorithm (Bell and Sejnowski, 1995) on preprocessed fMRI data with SPM8, and its implementation of group ICA in the fMRI toolbox (GIFT2.0; http://icatb.sourceforge.net). The ICA implementation procedures (see Supplementary material) allowed for the spatial independent components (ICs) to be extracted from the entire dataset. ICs were screened for goodness and reliability based on visual inspection and on the Iq index, which is considered a reliable measure of cluster stability (Himberg et al., 2004). We considered ICs with Iq index >0.7 to be reliable and stable (Ma et al., 2011). Based on these criteria, 35 ICs were extracted from the dataset.

To test our hypothesis and select the components of interest (COIs) for further investigation, we performed spatial correlations between IC spatial maps and two spatial templates. First, an attentional control network (ACN) template was built with the WFU Pickatlas Toolbox, which encompassed brain regions that were associated with the main effect of attentional control load in a previous study using the VAC (Blasi et al., 2007) and is consistently involved in attention (Casey et al., 2000; Fan