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Medial frontal gyrus alterations in schizophrenia: Relationship with duration of illness and executive dysfunction

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ABSTRACT

Executive functioning is consistently impaired in schizophrenia, and it has been associated with reduced gray matter volume in prefrontal areas. Abnormalities in prefrontal brain regions have also been related to the illness duration. The aim of the study was to investigate the effect of executive functioning decline and chronicity in prefrontal regions of patients with schizophrenia. Participants comprised 33 schizophrenic patients, 18 with duration of illness (DoI) shorter than 10 years and 15 with duration of illness longer than 10 years. In addition, 24 healthy controls served as a comparison group. Participants performed the Wisconsin Card Sorting Test (WCST) and underwent structural magnetic resonance imaging. Patients with longer DoI showed significant reduction of gray matter volume in the left medial frontal gyrus compared with healthy controls. Moreover, there was a trend for greater gray matter volume decrease in patients with a longer illness duration compared with patients with shorter illness duration. There was no interaction between the volume of the left medial frontal gyrus performance on the WCST. The present study supports the hypothesis that medial frontal gyrus alterations in schizophrenia are sensitive to duration of illness. These alterations were not associated with executive functioning.

1. Introduction

During the last two decades, voxel-based morphometry (VBM), a whole-brain automated method used to investigate regional brain functional and structural alterations (Ashburner and Friston, 2000), has been extensively applied to study the neuroanatomy of schizophrenia. The large number of individual studies has been recently reviewed in a voxel-based meta-analysis including 48 VBM studies (Bora et al., 2011). This study found that patients with schizophrenia have significant gray matter reductions compared with healthy controls, in the left and right insula, inferior frontal gyrus, bilateral thalamus and bilateral dorsal medial frontal gyrus/anterior cingulate. These gray matter abnormalities have been associated with the neurobiology of the disorder and they are also thought to underlie its clinical expression, including positive, negative, psychosocial and cognitive symptoms. In particular, there is specific evidence that cognitive dysfunctions are already evident in the early stages of the disorder, during the first episode of psychosis, and also during the prodromal phase (Fusar-Poli et al., 2012a). Recent studies suggest that patients with schizophrenia suffer from a "dysexecutive syndrome": independent of the executive task, patients with schizophrenia have consistently shown deficits in executive functioning when compared with a healthy control group (Raffard and Bayard, 2012). One of neuropsychological instruments most widely used to assess executive functioning in schizophrenia is the Wisconsin Card Sorting Test (WCST) (Nelson, 1976). The WCST is a multifactorial and complex test that involves different cognitive functions. In particular, capacity of 'working memory', along with attentive and executive functions, is considered a relevant factor responsible for the subjects' performance. Performance in the WCST is particularly impaired in schizophrenia (Heinrichs and Zakzanis, 1998), and it has been found to be associated with reduced gray

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matter volume in prefrontal areas (Seidman et al., 1994). A previous study (Rüsch et al., 2007), comparing patients with good versus poor WCST performance, found that prefrontal cortex abnormalities were related to WCST performance. This finding was subsequently confirmed by another study in which gray matter alterations in the prefrontal cortex were associated with poor performance on the WCST (Bonilha et al., 2008). Other studies, however, did not find associations between gray matter alterations and WCST performance in patients with schizophrenia, although they found relations with other neurocognitive tasks (Antonova et al., 2005; Premkumar et al., 2008; Segarra et al., 2008; Wolf et al., 2008). Considering the above findings, there is not yet consistent evidence indicating that prefrontal alterations in gray matter volume are directly related to WCST performance. The prefrontal cortex is strongly associated with cognitive deterioration in schizophrenia, but the dynamic process underlying such changes is relatively unaddressed (Cahn et al., 2002; van Haren et al., 2007).

Several factors, such as symptom severity and prolonged antipsychotic exposure, are known to influence the progressive brain changes observed in schizophrenia. Among these factors, the duration of illness is well known to play a significant role. Several studies investigated the association between the duration of illness and gray matter alterations, and the most consistent finding is a negative association with the volume of prefrontal (Molina et al., 2004; Premkumar et al., 2006; Tomelleri et al., 2009) and temporal regions (Hietala et al., 2003; Tomelleri et al., 2009).

The aim of the present study is to investigate the impact of duration of illness on gray matter volume and its relationship with executive functioning. We investigated this by comparing schizophrenia patients with more than 10 years' illness duration, schizophrenia patients with less than 10 years' illness duration and healthy controls. Our first hypothesis was that duration of illness would be associated with brain volume reductions, mostly in the prefrontal cortex (Molina et al., 2004; Premkumar et al., 2006; Tomelleri et al., 2009). Our second hypothesis was that there would be a significant interaction between duration of illness and executive dysfunction as measured by the performance on the WCST across our groups (Rüsch et al., 2007; Bonilha et al., 2008).

2. Methods

2.1. Subjects

Participants in the study comprised 33 patients with a diagnosis of schizophrenia (SCZ) and 24 healthy controls (HC). Among the patients, 28 were outpatients and 5 were inpatients. Both outpatients and inpatients were recruited through the Department of Neurology and Psychiatry, Sapienza University, in Rome. Patients were divided in two groups based on the duration of illness (DoI), which had a median value of 10 years: patients with shorter DoI (SCZ $\leq$ 10 years, $n=15$) and patients with longer DoI (SCZ $>$ 10 years, $n=18$). Healthy controls were recruited in the same catchment area. At study intake, two psychiatrists assessed patients with schizophrenia using the Structured Clinical Interview for DSM-IV (SCID-I) to confirm the diagnosis. Exclusion criteria for the patient group were as follows: deficits in general intelligence (IQ $<$ 70), neurological diseases, and diagnoses of psychotic disorders other than DSM-IV schizophrenia. Exclusion criteria for the control group were as follows: deficits in general intelligence (IQ $<$ 70), neurological diseases, Axis I or II psychiatric disorders, and first degree relatives with history of a psychiatric disorder. All patients had been on stable medications for at least two weeks at the time of the scanning (mean chlorpromazine equivalents 192.7 $\pm$ 226.9) (Ho et al., 2011).

2.2. Clinical measures

Patients were assessed on the day of the scanning using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1989). We additionally clustered the PANSS scores in line with the five-factor structure of the PANSS (Wallwork et al., 2012), which includes the Cognitive Factor (CogF) (Rodriguez-Jimenez et al., 2013). The CogF consists of three PANSS items: 'Conceptual disorganization' (P2), 'Difficulty in abstract thinking' (N5), and 'Poor attention' (G11). The CogF score was calculated for each subject. Patients were also assessed with the Global Assessment of Functioning (GAF).

2.3. Behavioral measures

Participants completed the computerized version of the WCST (Nelson, 1976). In this test each participant is asked to match test cards to reference cards according to the color, shape, or number of stimuli. Each participant is told to match the cards, but not how to match them. After each match, the participant is given feedback as to whether that match is right or wrong. After 10 correct matches, the rule is changed and the subject must learn again how to match the cards. The WCST is a measure of different cognitive processes such as attentive and executive functions. Traditionally, the WCST indexes cognitive flexibility, which is the ability to modify a behavioral response when the set changes. The number of completed categories (CAT), the number of perseverative responses (PR) and number of perseverative errors (PE) were considered performance measures. Perseveration is a characteristic trait of patients with schizophrenia (Koren et al., 1998), and it is a measure of the inability to adapt behavior to a new situation.

2.4. Image acquisition

All subjects underwent brain imaging using a Siemens Verio 3T MRI scanner at the Policlinico Umberto I, in Rome (Italy). T1 structural images encompassing the whole brain were collected from all subjects using the following parameters: repetition time=2300 ms; echo time =298 ms; inversion time =900 ms; flip angle=9°; slice thickness =1 mm; voxel size=1 × 1 × 1; number of slices=298.

2.5. Image analysis

Data were available for the entire sample. Group-related differences in gray matter volume (GMV) were examined using voxel-based morphometry (VBM), as implemented in SPM8 software (http://www.fil.ion.ucl.ac.uk/spm) running under MATLAB 8.1 (The MathWorks, Inc, Natick, MA). First, T1-weighted volumetric images were pre-processed using the diffeomorphic anatomical registration using exponentiated lie algebra (DARTEL) (Ashburner, 2007) SPM8 toolbox. This approach implicates the creation of a study-specific template and the segmentation of each individual image using this template, in order to maximize accuracy and sensitivity (Yassa and Stark, 2009). VBM pre-processing involved (1) checking for scanner artefacts and gross anatomical abnormalities for each subject, (2) setting the image origin to the anterior commissure, (3) using the DARTEL toolbox to produce a high dimensional normalization protocol (Yassa and Stark, 2009), (4) checking for homogeneity across the sample, and (5) using standard smoothing (i.e., 8 mm). A "modulation step" was also included in the normalization to preserve the information about the *absolute* gray matter values (Ashburner and Friston, 2000; Mechelli et al., 2005). After this pre-processing, smoothed, modulated, and normalized data were obtained which were used for the statistical analysis. Total intracranial volume was also calculated for all subjects.

An analysis of variance (ANOVA) was performed in SPM8 to compare the three groups in a whole brain analysis, with gender, age and years of education being entered as nuisance covariates. Statistical inferences were made at $p < 0.05$ after family-wise error (FWE) correction for multiple comparisons. To allow correlation analyses with psychotic symptoms and WCST performance, the eigenvariates (radius=8 mm) were extracted for each cluster of interest and correlated with each specific outcome. The presence of outliers was carefully checked by inspecting the regression scatterplots.

2.6. Statistical analysis

Due to drop-out of subjects (two controls and six patients refused further involvement in the study after the scanning), data for WCST performance were available for 22 controls and 27 patients. The GAF score was not available for two patients. Descriptive statistics were calculated for socio-demographic, clinical and behavioral variables. Between-group differences were addressed with analysis of variance (ANOVA) or *t*-test for continuous variables and with χ^2-test for categorical variables. An analysis of covariance (ANCOVA), with the age of the subject entered as a nuisance covariate, was performed to assess differences in WCST performance between the three groups. Post-hoc contrasts were corrected for multiple comparisons (i.e., Bonferroni correction). To better establish the magnitude of our findings, we computed the effect size by using the Cohen's *d*. Relationships between cognitive functioning and severity of symptoms and global functioning were investigated by correlating PANSS and GAF scores with WCST scores in the patient group as a whole (i.e., Pearson's *r*). GMV correlation analyses were conducted with the Spearman Rho in the entire sample, as data were not normally distributed, and with Pearson's *r* in each group; correction for multiple testing was obtained by dividing the value of the α-level (0.05) for the number of correlations conducted. Data were analyzed using IBM SPSS20.