European Neuropsychopharmacology (2009) **19**, 835–840

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Brain structural changes associated with chronicity and antipsychotic treatment in schizophrenia

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Received 24 June 2009; accepted 22 July 2009

KEYWORDS
MRI;
Imaging;
Frontal lobes;
Temporal lobes

Abstract

Accumulating evidence suggest a life-long impact of disease related mechanisms on brain structure in schizophrenia which may be modified by antipsychotic treatment. The aim of the present study was to investigate in a large sample of patients with schizophrenia the effect of illness duration and antipsychotic treatment on brain structure. Seventy-one schizophrenic patients and 79 age and gender matched healthy participants underwent brain magnetic resonance imaging (MRI). All images were processed with voxel based morphometry, using SPM5. Compared to healthy participants, patients showed decrements in gray matter volume in the left medial and left inferior frontal gyrus. In addition, duration of illness was negatively associated with gray matter volume in prefrontal regions bilaterally, in the temporal pole on the left and the caudal superior temporal gyrus on the right. Cumulative exposure to antipsychotics correlated positively with gray matter volumes in the cingulate gyrus for typical agents and in the thalamus for atypical drugs. These findings (a) indicate that structural abnormalities in prefrontal and temporal cortices in schizophrenia are progressive and, (b) suggest that antipsychotic medication has a significant impact on brain morphology.

1. Background

It is now generally recognized that schizophrenia is associated with brain structural abnormalities. However, at the present time, the effects of illness duration as well as medication on these morphological changes are still under

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doi:10.1016/j.euroneuro.2009.07.007

debate. Longitudinal neuroimaging studies have reported reduction in gray matter volume, particularly within the frontal lobes, in patients with chronic (Gur et al., 1998a; van Haren et al., 2007) and first-episode schizophrenia (Gur et al., 1998a; Lieberman et al., 2005; Hulshoff Pol and Kahn, 2008) over periods of 1–5 years. In addition, studies based on cross-sectional brain imaging data that examined patients with longer periods of illness (up to 40 years), have also found a negative correlation between chronicity and cortical volumes, particularly in the prefrontal cortex (Molina et al., 2004; Premkumar et al., 2006).

Emerging data suggest that antipsychotic medication may interact with disease mechanisms to delay, prevent or reverse the cortical volume loss (Lieberman et al., 2005; Dazzan et al., 2005; McCormick et al., 2005; Kopelman et al., 2005; Scherk and Falkai, 2006, Adams and Jayaram, 2007). This effect is thought to be more pronounced with atypical agents, which appear to preserve cortical gray matter volumes (Lieberman et al., 2005; van Haren et al., 2007), and not with typical antipsychotics (Scherk and Falkai, 2006). In order to disentangle the contribution of duration of illness and antipsychotic exposure we obtained structural Magnetic Resonance Imaging (MRI) data from a sample of 71 patients with schizophrenia recruited from the geographically defined catchment area of South Verona. Patients had variable illness duration and antipsychotic exposure. A group of 79 healthy volunteers were also included as comparison subjects. Our initial prediction was that (a) after controlling for antipsychotic exposure, illness duration will show an inverse correlation with frontal and temporal gray matter and (b) after controlling for illness duration, cumulative exposure to atypical antipsychotics would show a positive correlation with gray matter volume in the same regions.

2. Methods

2.1. Subjects

2.1.1. Patients

Seventy-one patients fulfilling Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV; American Psychiatric Association, 1994) for schizophrenia were recruited from the South Verona Psychiatric Case Register (Amaddeo et al., 1997; Tansella and Burti, 2003). The register includes information about patients residing in the epidemiologically defined catchment area of South Verona (with a population of approximately 100,000 inhabitants) and treated by the South Verona Community-based Mental Health Service (CMHS) and related clinics.

2.1.2. Healthy individuals

Seventy-nine individuals without any personal lifetime history of DMS-IV Axis I disorders were also recruited from the same catchment area. Exclusion criteria for all participants were (a) alcohol or substance abuse, within the preceding 6 months, as defined by the DSM-IV (b) any current major medical or neurological illness, (c) history of traumatic head injury with loss of consciousness, (d) DSM-IV axis I comorbidity. Additional exclusion criteria for comparison subjects were (a) any self-reported history of psychiatric disorders in first-degree relatives and (b) any prescribed medication.

2.2. Clinical assessment

Diagnostic evaluation was based on the Item Group Checklist of the Schedule for Clinical Assessment in Neuropsychiatry (IGC-SCAN) (World Health Organization, 1992). These assessments were conducted blind to diagnosis by trained clinical psychologists with extensive experience in using the SCAN. The Italian version of the SCAN was edited by our group (World Health Organization, 1996) and our investigators attended specific courses held by official trainers on how to administer this scale. The inter- and intra-rater reliability of the IGC-SCAN assessments was monitored by regular quality control meetings. Diagnostic validity was further confirmed by clinical consensus of two qualified psychiatrists.

Patients' psychopathology was rated with the Brief Psychiatric Rating Scale (BPRS 24-item version) (Ventura et al., 2000). Information about age of onset, duration of illness, and number of hospital admissions was obtained during interview and from medical records. Handedness was assessed with the Edinburgh Handedness Inventory (Oldfield, 1971). Duration of illness was calculated as the age of the patient minus the age of onset of the disorder. Age of onset was defined as the first time the patient had contact with psychiatric services for psychosis. Interview and case history reviews were conducted at the time of MRI acquisition, which included information on type, dose and lifetime exposure to antipsychotic medication. Four patients reported lifetime substance or alcohol abuse but none in the 6 months preceding their MRI examination.

Patients were divided into three groups based on their treatment at the time of the MRI scan, the unmedicated group, the group on atypical and the group on typical antipsychotics. Patients taking both typical and atypical agents were included in the typical group.

The study was approved by the Ethics Committee of the Azienda Ospedaliera of Verona. All participants provided signed informed consent, after having understood the nature and purpose of the study.

2.3. Neuroimaging image acquisition

MRI scans were acquired using a 1.5 T Siemens Magnetom Symphony Maestro Class, Syngo MR 2002B. All participants were provided with earplugs to reduce acoustic noise and their head was comfortably placed in a head holder and held stable in order to minimize movement artefact. Initially, exploratory T1-weighted images (TR = 450 ms, TE = 14 ms, flip angle = 90°, FOV = 230 × 230, slice thickness = 5 mm, matrix size = 384 × 512) were obtained to verify the subject's head position and the quality of the image. A sequence of DP/T2-weighted images were then obtained. (TR = 2500 ms, TE = 24/121 ms, flip angle = 180°, FOV = 230 × 230, slice thickness = 5 mm, matrix size = 410 × 512) according to an axial plane parallel to the anterior–posterior commissures (AC–PC), in order to exclude focal lesions. Subsequently, a coronal 3D MPR sequence was acquired (TR = 2060 ms, TE = 3.9 ms, flip angle = 15°, FOV = 176 × 235, slice thickness = 1.25 mm, matrix size = 270 × 512, TI = 1100) to obtain 144 images covering the entire brain.

2.4. Image analysis

Each subject's MRI dataset was normalised and segmented into gray matter (GM), white matter (WM) and cerebrovascular fluid (CSF) using unified segmentation (Ashburner and Friston, 2005) in SPM5 (http://www.fil.ion.ucl.ac.uk/spm/). Segmented images were modulated so that the intensity of each voxel represented a volume measure. Images were then smoothed using a Gaussian kernel of 12 mm full width half maximum and global tissue volumes were calculated by summing voxel values over each segmented image. Fractional tissue measures were then calculated by dividing gray, white matter and CSF volumes by the Total Intracranial Volume (TIV).

Smoothed gray matter segmented images were analysed using voxel based morphometry in SPM5. An analysis of covariance with TIV as a covariate and gender as additional factor was used to examine the effect of diagnosis (patients vs healthy participants) with a threshold of $p < 0.05$ family wise error (FWE). The relationship