Abstract Functional neuroimaging and neuropsychological performance indicate a prefrontal dysfunction in schizophrenia patients. Frontal morphological brain abnormalities are also evident in these patients, but the relationship between neuropsychology and neuroimaging findings remains unclear. In this study, thirty patients with schizophrenia and 30 control participants were assessed using a neuropsychological test battery sensitive to fronto-striatal system dysfunction. Computed tomography (CT) scans were used to calculate the distance from the corpus callosum to the frontal pole corrected for brain size (anterioposterior length) in the group of patients and in a group of control participants with negative radiological findings. Schizophrenia patients performed significantly worse than controls in all frontal lobe tests. Corrected length from the corpus callosum to the frontal pole was reduced in patients with schizophrenia. This easy-to-perform measurement has not been used in previous studies, and indicates that schizophrenia patients have structural frontal abnormalities. However, correlations between structural and functional measures fail to show a clear relationship between the prefrontal performance and the main CT measures. As a rule, the trend observed in the correlation matrix pointed towards a relationship between CT parameters and a dysfunction on neuropsychological tests sensitive to frontal lobe damage.

Key words schizophrenia · frontal lobe · neuropsychology · computerized tomography

Introduction

Schizophrenia symptoms have been associated with behavioral sequelae presented by patients with prefrontal lesions (Andreasen et al. 1986; Kurachi 2003). Negative symptoms have been linked with prefrontal cortex pathology (Weinberger et al. 1986, 1988; Wolkin et al. 1992; Velligan et al. 2002).

Frontal morphological brain abnormalities identified by computerized tomography (CT) and magnetic resonance imaging (MRI) are consistent findings in schizophrenia research (Andreasen et al. 1986; Shelton et al. 1988; Raine et al. 1992; Gur et al. 1998; Cahn et al. 2002). Linear measurements of ventricular size as a proportion of brain width were introduced to evaluate pneumoencephalograms. Evans (1942) by dividing the width of the anterior horns of the lateral ventricles by the maximum width of the brain, created a ratio to assess ventricular size. Similarly, Huckman et al. (1975) proposed an anterior horn span/brain width ratio for use with CT. These linear measurements, though are not very sensitive to subtle degrees of enlargement, are quick and simple to determine in clinical settings. In this regard, Shelton and Weinberger (1986) reviewed seven studies of ventricular enlargement size on CT in schizophrenia using linear measures, and they found that four (57 %) showed significant increase on lateral ventricles.

Since 1951, neuropsychological studies have provided clear, broad-ranging evidence of frontal lobe dysfunctions in schizophrenia patients (Fey 1951; Levin 1984; Seidman et al. 1992; Liddle and Morris 1991; Raine et al. 1992; Elliott et al. 1995; Hepp et al. 1996; Joyce et al. 1996; Pantelis et al. 1997; Lysaker et al. 2003). Finally, functional neuroimaging research using PET scan (Buchsbaum et al. 1992; Wolkin et al. 1992; Carter et al. 1997; Karlsson et al. 2002), SPECT and fMRI techniques have corroborated the involvement of prefrontal dys-
functions in this disease (Kumari et al. 2002; Ragland et al. 2004). However, the relationship between neuropsychology and neuroimaging findings remains unclear.

Several tests in neuropsychological batteries correlate with lateral ventricular enlargement. Golden et al. (1981) reported a positive correlation between ventricular enlargement and eight scales of the Luria-Nebraska Neuropsychological Battery (LNNB). Using the Wechsler Adult Intelligence Scale and the LNNB, Andreasen et al. (1986) and Kemali et al. (1985) reported similar results. Pandurangi et al. (1986) and Lawson et al. (1988) also found correlation between ventricular enlargement and poor performance on the Halstead-Reitan Neuropsychological Battery. However, other studies did not find any correlation between neuropsychological and neuroimaging parameters (Kolakowska et al. 1985; Obiols et al. 1987; Classen and Fritz 1988; Pfefferbaum 1988).

As for frontal lobe investigations, using stepwise regression analyses, Bilder et al. (1988) reported that ventricular enlargement and greater sulcal prominence predicted executive functions. Holm et al. (1995) also described a significant correlation between time taken to solve the Wisconsin Card Sorting Test (WCST) and ventricular volume in CT, and also found a trend towards a correlation between WCST perseverative errors and ventricular enlargement, as well as brain sulcal widening.

Using MRI, Raine et al. (1992) observed that schizophrenia patients had significantly smaller right and left prefrontal areas in all three MRI planes than normal and psychiatric control participants. Patients with schizophrenia also had significantly lower scores on prefrontal neuropsychological measures. However, the correlation between functional and structural prefrontal measures was not significant. More recently, Seidman et al. (1994) reported a significant correlation between the WCST performance and the dorsolateral prefrontal cortex area, and Perlstein et al. (2001) found that working memory dysfunction in patients with schizophrenia is caused by a disturbance of the dorsolateral prefrontal cortex and that this disturbance is selectively associated with cognitive disorganization.

Although MRI is superior to CT as a detector of subtle abnormalities, and allows three-dimensional studies of brain structures, linear measures on CT scan can focus on cerebral regions that can be crucial to pathogenesis. The frontal lobe is too large a region to be considered globally, the analysis needs to be based on the subdivisions of Mesulam (1990) or Damasio and Damasio (1993), the loops proposed by Alexander et al. (1986), developed by Cummings (1993), and updated by Teken and Cummings (2002) in the psychiatric population. According to Cummings's theory that draws on a synthesis of the main scientific findings of recent decades, the limbic frontal loop is associated with schizophrenia as well as the dorsolateral and the orbital areas. Against this background, we propose a very straightforward measure, which probably reflects atrophy in the paralimbic and orbital regions and can be easily replicated in other centers.

The aim of this study is to investigate frontal lobe alterations in a sample of chronic patients with schizophrenia, using linear CT scan parameters and a neuropsychological battery sensitive to damage in the main frontostriatal loops, in order to attempt to confirm the following hypotheses:

- Patients with schizophrenia show decrement in their frontobasal size and other brain dysmorphologies.
- Schizophrenia patients present cognitive impairment associate to frontostriatal dysfunction. Furthermore, there are significant correlates between functional and structural abnormalities in the frontal systems of schizophrenia patients.

**Methods**

**Participants**

The data for this research were obtained from a larger evaluation study (over a 3-year period from July 1988 to September 1991) of sex differences in alterations of brain structure and function of schizophrenia patients (Sanz 1996). The sample was a group of thirty schizophrenic inpatients (13 female and 17 male, admitted to the Psychiatric Hospital of Mérida, Spain), and two control groups of 30 healthy participants each. One control group participated in the study of neuropsychological variables, recruited from hospital employees, and the other in the CT study. The CT control group was selected from the neuroradiological databank of participants who referred headache and had negative radiological findings (this CT control group was included in order to reduce costs in the research and this design was considered from a statistical point of view). All participants were randomly selected and no significant differences between groups were found in age, gender, years of education and height. Patients were included if they had a diagnosis according to DSM-III-R criteria (APA 1987) and their course was chronic. All patients were routinely referred for a neuropsychological assessment at the study center and after complete description of the study to the participants, written informed consent was obtained. The schizophrenic spectrum subtype of the patients consisted of: 6 paranoid, 2 undifferentiated, 4 disorganized, and 18 residual. Tardive dyskinesia and associated psychopathological disorders were exclusion criteria in this group. Exclusion criteria for normal controls were a history of psychiatric or neurological disorder. All participants were between 21 and 48 years, literate, right handed and had normal or corrected to normal vision and hearing. Exclusion criteria for all participants were drug addiction, concomitant somatic disease, IQ < 75 or less than 6 years of education. Antipsychotic medication was converted to chlorpromazine dosage equivalences. Seventeen of the schizophrenia patients were taking anticholinergic medication at the time of study participation. The demographic and clinical characteristics of the samples are summarized in Table 1.

**Neuroimaging**

Computed tomography (CT) scans were obtained using a Philips tomoscan 350. Neuroimaging analysis was carried out using a customized "IMCO system analysis" developed by Kontron Bildanalyse Germany and a specific software package MIP-CNS. All measures of the CT scan slices were performed by two independent technicians, who could not recognize the scan of the patients versus the scan of the controls. To measure frontobasal size we calculated the distance from the corpus callosum to the frontal pole (FL). This measurement was corrected for brain size by means of the anteroposterior length (A-