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ORIGINAL PAPER

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Frontal lobe alterations in schizophrenia

Neuroimaging and neuropsychological findings

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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.

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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; Elliot 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 Fritze 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 Tekin 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 dysfunctioning. 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 schizophrenia 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 computerized "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 anterioposterior length (A-

Table 1 Clinical and demographic characteristics of the sample. Mean (standard deviation), t student test or χ^2

	Schizophrenia patients	Control participants cognitive tests	Control participants radiological file
Age	32.80 (6.738)	33.17 (5.590) t = –0.229 p = 0.819 ns	35.33 (5.616) t = –1.582 P = 0.119 ns
Education years	9.23 (8.83)	8.83 (2.198) t = 0.646 p = 0.521 ns	
Gender	17 male – 31 female	15 male – 15 female χ^2 = 0.268, p = 0.605 ns	15 male – 15 female χ^2 = 0.268, p = 0.605 ns
IQ (WAIS)	84.60 (17.272)	103.50 (13.673) t = 4.697 p = 0.000 significant	
Height	168.10 (6.397)		167.93 (5.884) t = 0.105 p = 0.917 ns
Chlorpromazine equivalence	516.17 (466.66)		
Anticholinergic (N = 14)	8.47 (12.138)		
PANSS positive	18.47 (4.783)		
PANSS negative	29.17 (5.937)		
PANSS composite	–10.70 (6.778)		

IQ Intelligence quotient; *WAIS* Wechsler Intelligence Scale for Adults; *PANSS* Positive and Negative Syndrome Scale; *ns* not significant

PL). The calculation of the prefrontal index (PI) was FL/A-PL (See Fig. 1).

We also added the classical measures of Evans's and Huckman's indexes. Evans's index was calculated by the quotient between the maximum external length of the frontal horns and the maximum internal diameter of the calota (Evans 1942). Huckman's index was estimated by adding the maximum and minimum external length of the frontal horns (Huckman et al. 1975). Furthermore, we calculated the surface of the cerebral parenchyma of the slice: brain area (BA) (Fig. 2).

Neuropsychological tests

In the neuropsychological assessment, we selected a test battery that covers the main fronto-striatal loops described by Cummings (1993). The tests administered were the following:

- *Wisconsin Card Sorting Test (WCST):* is a widely used tool which accurately recognizes frontal cortical dysfunction (Milner 1963; Robinson and Heaton 1980), particularly the DLPC (Goldberg et al. 1987; Rezai et al. 1993). The WCST was administered according to standardized criteria (Heaton 1981).
- *Stroop color word test:* Stroop test is a measure of perceptual interference, response inhibition, and selective attention. Impaired

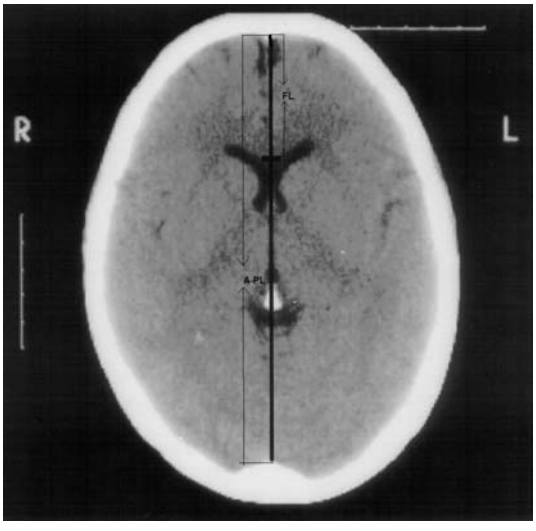

Fig. 1 Distance from corpus callosum to frontal pole (FL) and anterior-posterior length (A-PL)

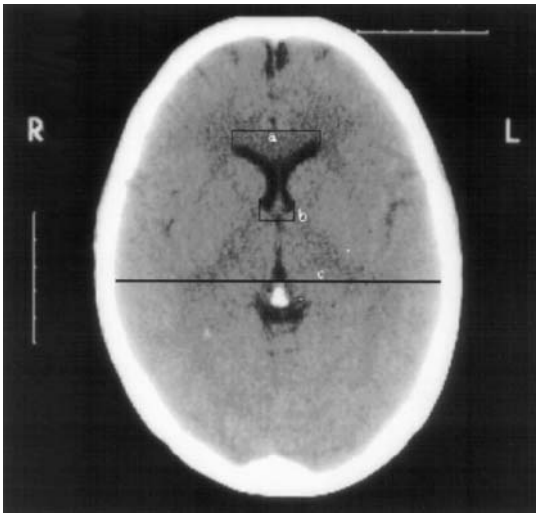

Fig. 2 Evans's and Huckman's indexes. (a: maximum external length of the frontal horns. b: minimum external length of the frontal horns. c: maximum internal diameter of the calota)

performance in Stroop test is closely associated with slowed rates of information processing in patients with left frontal lobe lesions, or bilateral lesions (Golden 1978; Stuss et al. 1983; Pardo et al. 1990).

- *Trail making test A and B:* This test, which consists of two parts (A and B), taps visual scanning, visuomotor and conceptual tracking, mental flexibility, and motor speed, and its performance is again associated with the frontal lobe system (Reitan and Wolfson 1985; Kolb and Whishaw 1983).
- *Chicago verbal fluency test:* Many studies have confirmed that verbal fluency is strongly connected with frontal lobe damage, particularly the left frontal lobe anterior to Broca's area (Ramier and Hecaen 1978; Kolb and Whishaw 1983).
- *Luria's premotor test:* The alterations in the motor sequence are linked to dysfunction localized in the areas of the frontal premotor cortex (Kolb and Whishaw 1983). This test belongs to Luria-Cristensen's neuropsychological research battery (Christensen 1974).

Psychopathology rating scales

The schizophrenia patients' clinical state was assessed using the Positive and Negative Syndrome Scale (Kay et al. 1986) on the day of testing. Ratings were completed by a Ph. D.-level psychologist and an experienced psychiatrist of the hospital's staff. Symptoms were grouped into three composite scores according to the manual (positive, negative and composite scales).

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS for Windows, 11.0). Kolmogorov-Smirnov goodness of fit test showed that the scores of the variables analyzed in this study did not deviate from normal distribution (except for Trail Making test A and B scores, which were logarithm transformed to normalize the score distribution before the statistical study). Furthermore, the neuropsychological data were converted to z scores. Therefore, parametric statistical methods were chosen. Group differences in CT and neuropsychological variables were analyzed by using Student's 't' tests and discriminant analysis. Two-tailed comparisons with significance level set at $p < 0.05$ were used. In order to control differences in IQ between groups, we performed covariate analysis. To study relations between values of the neuropsychological tests and the CT data, we calculated Pearson's correlations. P values less than 0.01 were interpreted as statistically significant. Relations of CT and neuropsychological tests with moderator variables such as symptoms, duration of illness and treatment with antipsychotic drugs, were analyzed using Pearson's correlations. P values less than 0.01 were interpreted as statistically significant.

Results

Neuroimaging findings.

Student's 't' tests data summarized in Table 2 reveal significant differences in the relative size of prefrontal measurements. The absolute length from the corpus callosum to the frontal pole was shorter in schizophrenia patients, and the differences in relation to the control group increased when the absolute frontal measure was corrected by the antero-posterior diameter. Classical ventricular measures: Evan's and Huckman's indexes, also differed significantly between groups. Furthermore, discriminant analysis showed that the five CT measures correctly identified 75.8 % of participants: 75 % of patients and 76.7 % of controls. In order of discriminant power, the parameters were: length of frontal lobe/cerebral diameter (0.64), Huckman's index (–0.61) and Evans's index (–0.50).

Table 2 t-test. Differences in CT measures between schizophrenia patients and controls

Group	Measure	Mean	SD	t	p
Sch	ba	28569.39	2500.36	0.42	ns
Con		28332.10	1783.79		
Sch	apd	208.07	9.88	0.40	ns
Con		207.13	7.96		
Sch	fll	66.53	2.35	–2.43	0.018
Con		69.40	2.36		
Sch	ifr	0.3207	0.17	–3.31	0.002
Con		0.3360	0.18		
Sch	Evans	0.2554	0.026	2.62	0.011
Con		0.2367	0.028		
Sch	Huckman	45.3429	4.712	3.16	0.003
Con		40.8367	6.007		

Sch schizophrenia patients; *Con* control participants; *ns* not significant; *ba* brain area; *apd* antero-posterior diameter; *fll* length of frontal lobe (from corpus callosum to frontal pole); *ifr* fll/apd; *Evans* Evans' index; *Huckman* Huckman's number

Neuropsychological findings and CT scan correlates

Table 3 gives Student's 't' test analysis. Patients performed worse than controls on all frontal lobe tests administered. After covariate analysis to control the effects of the general intelligence quotient, WCST, Stroop test and Trail Making A test remained statistically significant. Likewise, the neuropsychological battery used correctly classified 93.3 % of schizophrenia patients and 100 % of controls in the discriminant analysis. In order of discriminant power, the frontal tests used were: Stroop test-color (–0.65), Stroop test-interference (–0.63), WCST categories completed (–0.59), WCST % of errors (0.56), Stroop test-color/word (–0.55), WCST % of correct answers (–0.52) and WCST % of perseverative answers (0.52). The neuropsychological data were transformed to z scores in order to compare frontal lobe measures. To determine the percentage of patients impaired on a specific measure, we took the reference of 1 SD from the mean of the control group. The Wisconsin Card Sorting Test (WCST) was the most sensitive test for schizophrenia: 80 % of patients had abnormal performance in the WCST categories and 83 % showed more perseverative responses. Seventy-six percent of patients had abnormal performance on the Stroop Test (Colour-Word). Sixty-three percent revealed poor performance in Trail-Making A, and 50 % had abnormal values on the Trail-Making-B. Thirty-three percent of patients showed less fluency on Chicago Verbal Fluency Tests, and finally, 26 % of schizophrenic patients showed poor performance in Luria's premotor test.

Finally, in order to investigate relationships between TC scans and the cognitive test data, we performed Pear-

Table 3 Cognitive measures of frontal lobe

Group	Test	Mean	SD	t	p	Covariate by IQ F	Covariate by IQ p
	WCST scores						
Sch	No. of categories achieved	2.40	2.09	−8.00	< 0.001	30.43	< 0.001
Con		5.73	0.90				
Sch	% correct answers	51.16	20.15	−7.07	< 0.001	23.17	< 0.001
Con		79.23	8.14				
Sch	% errors	49.36	19.31	7.61	< 0.001	27.75	< 0.001
Con		20.43	7.81				
Sch	% perseverative answers	48.53	26.43	7.04	< 0.001	23.68	< 0.001
Con		12.23	9.93				
	Stroop test scores						
Sch	Word	78.70	20.01	−6.06	< 0.001	13.12	0.001
Con		104.40	11.77				
Sch	Color	44.40	13.67	−8.92	< 0.001	41.76	< 0.001
Con		40.26	9.83				
Sch	color/word	25.23	7.98	−7.47	< 0.001	27.26	< 0.001
Con		40.26	7.60				
Sch	interference	28.03	7.78	−8.59	< 0.001	37.04	< 0.001
Con		42.36	4.78				
	Trail Making Test scores						
Sch	Part A (time)	1.846	0.262	5.01	< 0.001	4.25	0.04
Con		1.572	0.145				
Sch	Part B (time)	2.300	0.315	4.24	< 0.001	0.023	ns
Con		2.011	0.198				
	Verbal Fluency scores						
Sch		27.66	16.27	−2.61	0.012	2.49	ns
Con		39.06	17.57				
	Luria Task scores						
Sch	No. correct	17.96	2.20	−3.33	0.002	1.09	ns
Con		19.36	0.66				
Sch	time	43.00	16.48	3.71	0.001	2.84	ns
Con		31.16	5.82				

Sch schizophrenia patients; *Con* control participants; *ns* not significant

son's correlations between values of the neuropsychological tests and the CT data. The results are summarized in Table 4. Taking a $p < 0.01$, we only found a negative correlation between the anterior-posterior diameter and Trail Making test forms A and B.

Moderator variables

In order to study possible relations of symptoms, duration of illness, and antipsychotic medication (transformed in dosage of chlorpromacine equivalences) with CT parameters and neuropsychological measures, we performed Pearson correlations. Our neuroimaging and neuropsychological results were not meaningfully related to the moderator variables (Table 5).

Discussion

The results of this study add more evidence to the growing body of data that implicate the frontal system as a possible locus for the abnormalities observed in patients suffering from schizophrenia. The main finding is the existence of a significant decrease in frontal lobe length (distance from corpus callosum to frontal pole) of the schizophrenia patients studied. The decrease is greater when brain size is controlled using the brain diameter measure. As far as we know, this measure has not been used in previous studies, and we think that it is an easy to perform and reliable method for assessing structural frontal alterations in schizophrenia, which can be easily replicable in clinical settings. Moreover, we found significant differences in Huckman's and Evans's indexes that tend to confirm the existence of a greater lateral ventricular enlargement in patients with schizophrenia in comparison to healthy participants. This second finding has been extensively reported in previous CT and MRI studies on this disorder (Pfefferbaum and Zyprusky 1991).

Although brain abnormalities in schizophrenia are subtle and the average magnitude of difference between patients and controls is generally too modest to support the idea that the decrement of frontal brain volume is a necessary component of schizophrenia (Zakzanis and Heinrich 1999), the development of more advanced and accurate measurement tools in neuroimaging are providing increasing evidence for frontal lobe abnormali-

Table 4 Pearson correlations of CT and neuropsychological measures

	BA	APD	FLL	IFR	EVANS	HUCKMAN
WCST categories achieved	0.417*	0.397*	0.137	–0.212	0.176	0.154
	0.27	0.36	0.487	0.279	0.372	0.435
WCST correct answers	0.241	0.181	–0.009	–0.201	0.110	0.099
	0.216	0.357	0.963	0.301	0.576	0.616
WCST error	–0.36	–0.22	0.006	0.65	0.115	0.109
	0.854	0.911	0.987	0.744	0.561	0.580
WCST perseverative	–0.212	–0.112	0.25	0.147	0.24	–0.111
	0.280	0.570	0.898	0.445	0.905	0.573
Stroop test word	0.124	0.168	0.377*	0.287	–0.002	–0.096
	0.529	0.392	0.048	0.138	0.992	0.626
Stroop test color	0.187	0.339	0.317	0.49	–0.091	–0.310
	0.340	0.077	0.100	0.806	0.644	0.108
Stroop test color word	0.307	0.447*	0.188	–0.198	–0.018	–0.154
	0.112	0.017	0.339	0.313	0.927	0.435
Stroop test interference	0.183	0.309	0.359	0.131	–0.057	–0.250
	0.381	0.112	0.061	0.507	0.774	0.199
Trail Making test A	–0.376*	–0.623**	–0.273	0.243	0.135	0.610
	0.049	0.000	0.159	0.213	0.495	0.759
Trail Making test B	–0.433*	–0.639**	–0.269	0.267	–0.77	0.033
	0.021	0.000	0.167	0.169	0.695	0.868
Verbal fluency test	0.227	0.352	0.273	–0.051	–0.229	–0.284
	0.245	0.066	0.159	0.746	0.241	0.143
Luria: correct answers	0.209	0.304	0.016	–0.295	–0.212	–0.249
	0.286	0.116	0.935	0.128	0.278	0.129
Luria: time invested	0.087	0.057	0.033	0.042	0.120	0.202
	0.660	0.774	0.864	0.832	0.543	0.302

* $p < 0.05$; ** $p < 0.01$

BA brain area; *APD* antero-posterior diameter; *FLL* length of frontal lobe (from corpus callosum to frontal pole); *IFR* fll/apd; *EVANS* Evans' index; *HUCKMAN* Huckman's number

ties, particularly prefrontal grey matter and orbitofrontal regions (Shenton et al. 2001). However, patient sample characteristics, including sample size, handedness and gender composition, emerged frequently as moderators of brain-imaging effects sizes (Davidson and Heinrich 2003). Considering that we used a straightforward and no oversensitive neuroimaging measure, our positive results seem to be more outstanding. These findings can not be explained by differences in sex, age, handedness, body size, or cranial-cerebral size. Furthermore, other moderator variables as medication, symptoms and duration of illness were also controlled.

Although frontal lobe dysfunction in schizophrenia patients is generally considered to be a secondary effect of meso-limbic system pathology (Goldman-Rakic and Selemon 1997), the decrement of frontal lobe length observed in our research also suggests an intrinsic disorder in the frontal lobe, probably related to hypoplasia or brain atrophy. Dysmorphology in the frontal structures was previously reported by an elegant MRI research of Andreasen et al. (1986) and confirmed in the 59% of papers reviewed by Shenton et al. (2001).

Our findings in the neuropsychological tests are consistent. Globally, the five tests discriminate 95% of participants. Our results are in agreement with those reported by Kolb and Whishaw (1983), who observed dysfunction in four tests sensitive to prefrontal dorsolateral and orbital regions in schizophrenia patients. Other more recent studies have also replicated these findings (Pantelis and Nelson 1994; Rubin et al. 1995). Patients with schizophrenia performed worse than normal controls on the WCST and the Stroop test, even controlling for the general intelligence quotient. Similar results have been reported by other studies (Fey 1951; Berman et al. 1986; Weinberger et al. 1986; Seidman et al. 1992; Hepp et al. 1996; Carter et al. 1997). Although the patients performed worse in other frontal measures, there were no significant differences with the control group when general intelligence quotient was introduced as a covariant. In this regard, previous studies reviewed show that mean value of general intelligence functioning is lower in the group of patients with schizophrenia compared with normal controls. IQ scores of patient's groups ranged between 98 and 76 (Kashima 1987; Bilder et al. 1988; Lawson et al. 1988).

Correlations between structural and functional measures fail to show a clear and strong generalized correlation between the prefrontal performance and the main CT parameters. Nevertheless, as a rule, the trend observed in the correlation matrix pointed towards a relationship between alterations in CT measures and a poor performance on neuropsychological tests sensitive to fronto-striatal functioning. Furthermore, the mentioned trend had no substantial modifications when the scores of cognitive test where corrected for IQ. The neu-

Table 5 Pearson correlations of CT scans, cognitive tests and moderator variables

	Illness duration	Antipsychotic medication	PANSS positive scale	PANSS negative scale	PANSS composite scale
BA	–0.208 0.288	0.085 0.668	–0.338 0.79	0.080 0.687	–0.291 0.133
APD	–0.187 0.352	–0.005 0.981	–0.83 0.352	0.028 0.888	–0.144 0.464
FLL	–0.234 0.230	0.005 0.981	–0.200 0.307	0.126 0.522	–0.241 0.217
IFR	–0.153 0.436	0.025 0.898	–0.68 0.732	0.134 0.446	–0.161 0.414
Evans	–0.453* 0.016	–0.046 0.815	0.230 0.239	0.363 0.058	–0.186 0.344
Huckman	–0.397* 0.036	0.014 0.945	0.025 0.900	0.321 0.096	–0.288 0.137
WCST categories	–0.417* 0.022	–0.370* 0.044	–0.195 0.302	0.019 0.919	0.120 0.526
WCST correct	–0.435* 0.016	–0.335 0.071	0.087 0.646	0.004 0.984	–0.065 0.733
WCST error	0.433* 0.017	0.343 0.063	0.130 0.493	–0.010 0.900	0.100 0.589
WCST perseverations	0.443* 0.014	0.263 0.161	0.078 0.881	0.099 0.603	–0.032 0.869
Stroop test word	–0.136 0.472	0.037 0.847	–0.248 0.187	–0.250 0.182	0.044 0.816
Stroop test color	0.091 0.632	0.002 0.990	–0.148 0.432	–0.182 0.330	0.054 0.775
Stroop test color word	0.056 0.770	–0.051 0.789	–0.270 0.149	–0.246 0.190	0.025 0.897
Stroop test interference	0.016 0.932	0.011 0.954	–0.194 0.305	–0.206 0.275	0.044 0.819
Trail Making test A	0.042 0.827	0.198 0.317	0.292 0.117	0.344 0.063	–0.095 0.618
Trail Making test B	0.359 0.051	0.347 0.060	0.289 0.121	0.204 0.280	0.026 0.893
Verbal fluency	–0.117 0.539	–0.231 0.220	–0.165 0.383	–0.176 0.353	0.037 0.845
Luria correct	–0.007 0.969	0.049 0.796	–0.286 0.125	–0.258 0.169	0.024 0.901
Luria time	0.206 0.275	0.269 0.151	0.227 0.229	0.377* 0.04	–0.170 0.362

* $p < 0.05$; ** $p < 0.01$

BA brain area; *APD* antero-posterior diameter; *FLL* length of frontal lobe (from corpus callosum to frontal pole); *IFR* fll/apd; *Evans* Evans' index; *Huckman* Huckman's number; *PANSS* Positive and Negative Syndrome Scale

ropsychological dysfunction pattern was shown to relate to decreased anteroposterior diameter and to the structure of the cerebral parenchyma, which could be characteristic of cerebral hypoplasia (Andreasen et al. 1986), but our findings in this question are not specific of the frontal lobe alterations. Although they showed separately as frontal lobe decrease in CT, as cognitive impairment in the neuropsychological tests, our method is probably not accurate enough to detect a clearer pattern of correlation between these two dimensions. Until now, the only measure which has been reported to be sensitive enough to distinguish clearly between patients' and controls' distributions is the functional neuroimaging of the frontal lobe while participants are performing an experimentally controlled task (Zakzanis and Heinrich 1999; Semkovska et al. 2001).

Related to the moderator variables, we did not find a significant correlation between negative symptoms, alterations in CT and cognitive measures in schizophrenia patients. We only observed a moderate relationship between duration of illness and the cognitive impairment in executive functions associated to prefrontal lobe. Likewise, we also found a moderate correlation between duration of illness and increased size of ventricular enlargement in CT scans of patients. Some studies have not found a correlation between symptoms and frontal abnormalities (Rubin et al. 1995; Malla et al. 2002); on the other hand and following Liddle's (1991) hypothesis, Semkovska et al. (2001), Sanfilipo et al. (2002) have observed correlations between negative symptoms and selective prefrontal alterations in schizophrenia patients. Furthermore, Malla et al. (2002) reported that patients

with a first episode of schizophrenia showed evidence of morphological changes generally associated with chronic schizophrenia that were not likely related to duration of illness. The epidemiology of the observed alterations probably supports a developmental origin, perhaps with limited progressive change beyond that expected in normal aging. Establishing the clinical significance of relative, static structural brain dysmorphologies remains a major challenge that may best use combined cross-sectional and longitudinal study designs (Pfefferbaum and Zyprusky 1991).

This research has limitations including the quite simple method of neuroimaging assessment, and the inclusion of two control groups, but on the other hand, this easy-to-perform measurement has not been used in previous studies, and it suggests that schizophrenia patients have functional and structural frontal abnormalities in their brains. We think that our study could provide a non-expensive, quick and straightforward method for research at clinical centers that do not have sophisticated and costly devices. As schizophrenia patients show substantial heterogeneity, large samples are needed to study the full implication of brain pathomorphology, and this neuroimaging measure can be used routinely to obtain a large number of scans for study. Furthermore, it could be a promising method for future research using more accurate neuroimaging techniques as fMRI with cognitive activation tasks.

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