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Cerebral metabolic patterns in chronic and recent-onset schizophrenia

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Abstract

This article compares the effects of short- and long-term treatment with haloperidol in schizophrenic patients, with the aim of identifying brain metabolic activity patterns common to acute and chronic patients in spite of their different treatment and illness duration. [18F]fluoro-deoxy-glucose (FDG)-positron emission tomography (PET) studies in the resting condition were performed on 18 healthy controls and two groups of schizophrenic patients: recent onset (RO, $n=17$) minimally treated with haloperidol, and chronic long-term treated patients (LT, $n=34$). PET scans were analyzed using statistical parametric mapping (SPM'99) and the *P*-value threshold to assess differences between groups was validated by bootstrapping techniques. Our results show a distinctive pattern of decreased activation of the visual cortex in RO and LT patients, when compared to healthy controls. Insular hypometabolism and a certain degree of hypofrontality were observed in the LT group when compared to RO patients. The main effect of the long-term administration of haloperidol seems to be an increase of cerebellar, basal ganglia and motor area metabolism.

Keywords: Positron emission tomography (PET); Fluoro-deoxy-glucose (FDG); Neuroleptics; Haloperidol; Statistical parametric mapping (SPM)

1. Introduction

There is a large body of evidence describing functional alterations of the brain associated with schizophrenia. Over the last decade, several studies using positron emission tomography (PET) support the existence of cortical and subcortical dysfunctions in this disease (Buchsbaum et al., 1998). However, the interpretation of PET data in schizophrenia is compromised by at least two confounding factors that alter brain metabolism: the treatment with neuroleptics and the cognitive condition of the subjects during the scan.

The acute or chronic administration of neuroleptics is well known to influence regional cerebral

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activity (Miller et al., 1997). At least two effects seem clearly attributable to neuroleptic administration. First, a decrease in cortical activity, especially in the frontal lobe, detected even after short-term administration (Holcomb et al., 1996; Wolkin et al., 1996). Second, an increase of subcortical activity, largely replicated both after long- (DeLisi et al., 1985; Buchsbaum et al., 1987; Szechtman et al., 1988; Holcomb et al., 1996) and short-term administration (Bartlett et al., 1994).

It is unclear, however, if long-term treatment may lead to different effects on frontal activity than acute administration. A study in monozygotic twins concordant for schizophrenia demonstrated that the twins cumulatively receiving the higher doses of neuroleptics were more hyperfrontal (Berman et al., 1992). Such resting 'hyperfrontality' may be related to schizophrenia itself, as reported in neuroleptic-naive (Catafau et al., 1994) or previously treated (Szechtman et al., 1988) patients, also being associated with the severity of symptoms (Ngan et al., 2002).

The effect of the cognitive condition during the PET scan may interact with the effect of the treatment. For instance, the expected decrease in global activity induced by haloperidol (Bartlett et al., 1994; Holcomb et al., 1996; Wolkin et al., 1996) can be overlapped by the increase of activity caused by the use of cognitive paradigms during the PET scan. In this regard, the analysis of PET scans of patients in a resting condition may complement the information obtained during cognitive activation. It is, moreover, conceivable that a hyperfrontal resting state might lead to a state of decreased potential for an adequate activation during the corresponding tasks, as suggested by the results of Catafau et al. (1994).

Other factors, such as morphological and long-term neurochemical changes, may compromise the interpretation of the resting metabolic findings in chronic schizophrenia. The comparison of samples with and without these confounding factors and those derived from different treatment durations may help to elucidate the existence of common findings attributable to schizophrenia.

These facts put forward the interest of comparing patients with short- and long-term haloperidol treatment, to understand its mechanism of action and its relation with other alterations caused by schizophrenia. Our study investigated these questions using (FDG) PET images obtained in the resting condition in two groups of patients (short-term and long-term haloperidol treatment) and a matched control group. The study was analyzed using SPM methods and validated the SPM significance threshold by means of resampling techniques.

2. Methods

2.1. Subjects

A total of 51 schizophrenic patients (DSM-IV) and 18 control volunteers were studied. Patients were divided into two groups: recent onset (RO, $n=17$, 14 males, all paranoid) and long-term treated patients (LT, $n=34$, 21 males; 32 paranoids and two undifferentiated). The RO group included patients with an illness onset up to 3 years before their first visit to the psychiatrist. All these RO patients only received a minimal treatment of 5 mg/day of haloperidol for 2 days before the PET study, ceasing 12 h before undergoing the scan. The group of LT patients had received different typical antipsychotics during their illness. To homogenize treatment conditions, LT patients were switched to a standard treatment of haloperidol (10 mg/day) for at least 4 weeks before the first PET scan, and in the morning of the study day they received the last dose.

SANS and SAPS scales were used for the evaluation of symptoms, and diagnosis was confirmed using the SCID interview (Patient version). Illness onset was defined as the earliest documented time at which the patient met the schizophrenia criteria of DSM-IV. Because of the nature of the patient groups, illness duration was significantly longer in LT patients than in the RO group ($t=5{,}09$, d.f. $=49$, $P<0.001$). There were also age differences, LT patients being significantly older than the RO patients ($t=4{,}37$, d.f. $=49$, $P<0.001$). No significant differences were observed in any of the symptom scores (Table 1).

Any antecedent of psychiatric disorder or treatment was excluded in control subjects. Educational status lower than college level was required in

Table 1
Mean (standard deviation) of clinical SAPS and SANS scores, and demographic characteristics of the patient and control groups

	Recent onset ($n=17$)	Long-term ($n=34$)	Controls ($n=18$)
Age (years)	23.68 (4.04)	36.05 (12.53)	29.63 (9.87)
Education (years)	10.19 (3.51)	9.39 (2.74)	11.94 (3.39)
Parental socio-economic status	1.9 (0.9)	2.0 (1.0)	2.1 (0.9)
Height (cm)	171.05 (9.13)	167.85 (9.70)	169.38 (12.11)
Duration (years)	1.16 (0.87)	11.26 (10.30)	
Age at onset (years)	24.76 (8.17)	24.11 (5.88)	
Hallucinations	8.58 (6.09)	9.96 (5.49)	
Delusions	16.44 (8.98)	18.56 (9.20)	
Bizarre behavior	5.26 (3.91)	5.75 (3.99)	
Thought disorder	5.97 (5.71)	9.37 (6.96)	
Alogia	5.40 (5.38)	8.37 (6.33)	
Affective blunting	11.86 (9.88)	14.21 (8.46)	
Apathy	6.70 (4.40)	8.18 (4.41)	
Anhedonia	12.12 (7.98)	14.00 (5.60)	
Attention	2.88 (2.09)	3.37 (2.98)	

order to properly match the patient group. Neither height nor educational level differed significantly between patients and control subjects (Table 1). No differences in parental education or socioeconomic status (Hollingshead and Frederick, 1953) were observed between patients and controls.

Exclusion criteria for both patients and controls were as follows: neurological illness, history of cranial trauma with loss of consciousness, past or present substance abuse excluding nicotine or caffeine or any current treatment with known CNS action. All patients and controls also underwent an MRI scan to exclude any clinically relevant abnormality as judged by an expert radiologist blind to the diagnosis.

After complete description of the study to the subjects, written informed consent was obtained from each patient and from a first-degree relative. The research and ethical boards of the participant institutions endorsed the study.

2.2. PET procedure

PET studies were obtained with a Posicam EZL PET scanner 20 min after the injection of 370 MBq of 18-FDG. Matrix size was $256\times256\times61$, and slices were 2.6 mm thick. Subjects were instructed to lie down in a supine position in a dark and silent room with eyes open and ears unplugged from 10 min before FDG administration and for 20 additional minutes before image acquisition. They did not receive any special instruction except to try to keep as relaxed as possible. The PET study was performed after a fasting period of over 6 h. Coffee and psychoactive beverages were not allowed.

2.2.1. Image analysis

PET images were analyzed with the SPM99 software package (from the Welcome Department of Cognitive Neurology, London, UK) (Frackowiak et al., 1997). Studies were transformed into Talairach stereotactic space (Talairach and Tournoux, 1988) warping each scan to a reference template image that already conformed to the standard space. Images were reformatted to a final voxel size of $2\times2\times2$ mm and smoothed using an isotropic Gaussian kernel of $12\times12\times12$ mm FWHM. The gray-level threshold was set to 0.8, i.e. only voxels with an intensity level above 0.8 of the mean level for that scan were included in the statistical analysis.

2.3. Statistics

The intensity normalization method used to remove the confounding effect of intersubject dif-

ferences in global activity was ANCOVA. This method provided the best results in terms of variance stabilization, being the grand mean of CVs (coefficient of variation) of the residuals of the statistical model lower (0.1111) than that provided by proportional scaling (0.1139).

The statistical model used in the SPM analysis was an ANCOVA of three groups using age as a covariate. Comparisons among groups were performed by defining the appropriate contrasts in the SPM design. Considering the three groups of subjects (controls, RO, LT), common differences between controls and all schizophrenic patients were assessed with the contrasts (2, −1, −1) (testing hyper-activations in controls) and (−2, 1, 1) (testing hyper-activations in patients), whereas for testing differences between patient groups, the contrasts (0, 1, −1) and (0, −1, 1) were applied.

Setting the proper thresholds to consider an observed *P*-value as significant is critical in these type of studies (Andreasen, 1996). For this reason, we carried out a validation procedure to determine the adequate level of significance for our data. Assuming that no significant differences should be expected within the control group, we used a bootstrap random resampling technique to extract 200 random subgroups on which we performed the same tests as on the patient groups (Efron and Tibshirani, 1986). This procedure provided an empirical validation of the significance levels used throughout the study.

The clinical significance of the changes in metabolism is graded into three different levels of evidence: L1, peak-height corrected *P*-value below 0.05; L2, extent-corrected *P*-value below 0.05; and L3, uncorrected *P*-value below 0.001. These levels of significance allow us to label those clusters that also meet more restrictive criteria beyond the uncorrected *P*-level of ($P < 0.001$), thus highlighting stronger effects and facilitating the comparison with other studies that make use of alternative thresholds equivalent to our L1 and L2.

3. Results

Results are presented as statistical maps showing pixels with an uncorrected *P*-value above $P < 0.001$ (L3 criterion) overlaid on an MRI template (the T1 weighted anatomical image of SPM99). Table 2 summarizes the results of the different comparisons, indicating regions with significant differences, the SPM coordinates of its statistical maximum, the number of voxels, its *z*-score and the evidence criteria as defined above.

3.1. Schizophrenic patients vs. control subjects

The control group showed higher metabolism in the visual cortex and bilateral insula (Fig. 1). Patients showed higher metabolism in motor area (bilateral) and bilateral inferior temporal areas and cerebellum (Figs. 2 and 5).

3.2. LT vs. RO patients

This comparison revealed higher metabolism in long-term patients (LT) in motor and inferior temporal areas as well as in pallidum/putamen, and cerebellum (Fig. 3). Recent onset patients (RO) showed higher metabolism in the insula, bilateral dorsolateral prefrontal cortex and anterior cingulate (Figs. 4 and 5).

4. Discussion

4.1. Differences attributable to long-term vs. short-term haloperidol treatment

In our study, hyperactivity of the motor area and cerebellum was found in the comparison between patients and controls and also in the comparison between RO and LT patients. This finding is probably an effect of long-term haloperidol treatment. Motor side effects of classical neuroleptics have been directly related to the activity of the motor cortex (Molina Rodriguez et al., 1997).

On the other hand, the cerebellum is a key element of the motor system (Fox and Williams, 1970). An increase of cerebellar activity with haloperidol was described by Bartlett et al. (1994), allowing us to relate the higher metabolism in LT patients with longer treatment. Although Barlett's study was performed in healthy volunteers, it is likely that the same effect would be observed in patients because this increase has not been

Table 2
Regions showing significant differences of activity for each group comparison

Region	*x,y,z*	Z_{max}	N_{vox}	LOE
Ctrl ($N=18$) > Schi ($N=17+34$) (Figs. 1 and 5)				
Primary visual	16, −66, −4	3.74	114	L3
Insula (L)	42, 14, 0	3.71	129	L3
Insula (R)	−38, 20, 2	3.49	23	L3
Ctrl ($N=18$) < Schi ($N=17+34$) (Figs. 2 and 5)				
Motor (L and R)	−8, −28, 70	5.05	10 187	L1
Inferior temporal (R)	−40, 6, −38	4.31	390	L3
Inferior temporal (L)	44, 2, −36	3.99	264	L3
Cerebellum (R)	−40, −66, −38	3.54	456	L3
Cerebellum (M)	−2, −70, −42	3.35	327	L3
LT ($N=34$) > RO ($N=17$) (Fig. 3)				
Motor (R)	−14, −32, 48	5.43	1556	L1
Motor (L)	16, −46, 58	4.93	1489	L1
Cerebellum (M)	8, −70, −48	3.96	836	L2
Cerebellum (L)	18, −36, −44	3.95	226	L3
Inferior temporal (L)	34, −14, −32	3.74	331	L3
Cerebellum (R)	−14, −38, −40	3.73	286	L3
Pallidum/putamen (R)	−22, 2, −12	3.65	128	L3
Inferior temporal (R)	−42, −28, −24	3.63	217	L3
Pallidum/putamen (L)	36, −2, −2	3.56	186	L3
LT ($N=34$) < RO ($N=17$) (Fig. 4)				
Insula (R)	−40, 18, 6	4.14	346	L3
Anterior cingulate	−2, 34, 40	4.01	481	L3
Dorsolateral prefrontal (L)	34, 50, 10	3.96	499	L3
Dorsolateral prefrontal (L)	56, 22, 26	3.65	139	L3
DLPF (R)	−50, 12, 26	3.24	31	L3

For each region, the table shows the SPM coordinates of the maximum, its *z*-value, the number of voxels and the level of evidence. Levels of evidence (LOE) are: L1, peak-height corrected *P*-value lower than $P<0.05$; L2, extent-corrected *P*-value lower than $P<0.05$; L3, uncorrected *P*-value below $P<0.001$ (see Section 2 for details). The figure showing the corresponding SPM maps are indicated.

described as a trait of schizophrenia. In addition, our results show that the magnitude of the differences between LT and RO groups in the cerebellum was similar to that found in the motor cortex.

Classical neuroleptics are known to increase basal ganglia activity (DeLisi et al., 1985; Buchsbaum et al., 1987; Bartlett et al., 1994; Holcomb et al., 1996), which is consistent with the higher

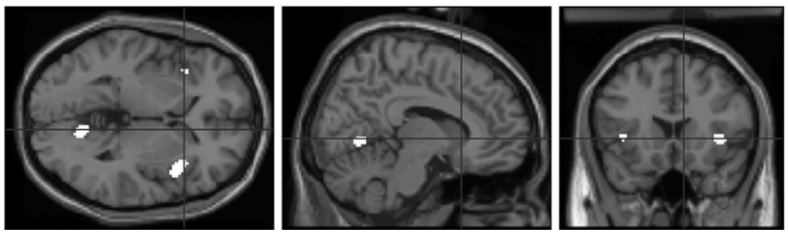

Fig. 1. Regions with significantly decreased metabolic activity in patients as compared with controls: primary visual and bilateral insula.

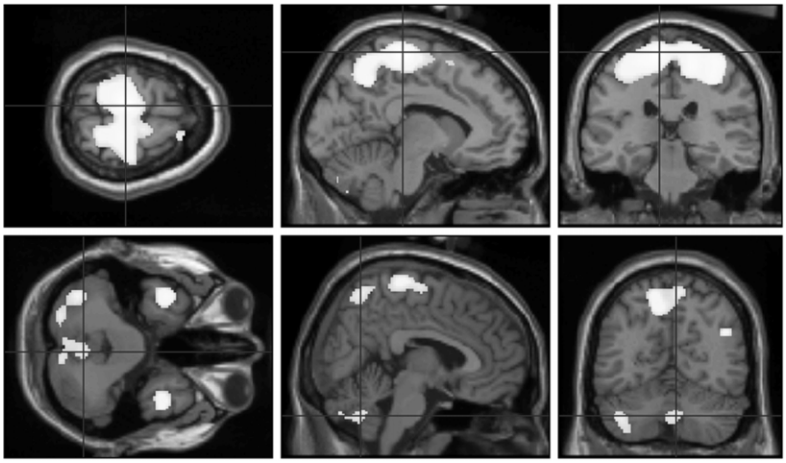

Fig. 2. Regions with significantly higher activity in patients as compared with controls: primary motor, cerebellum and inferior temporal.

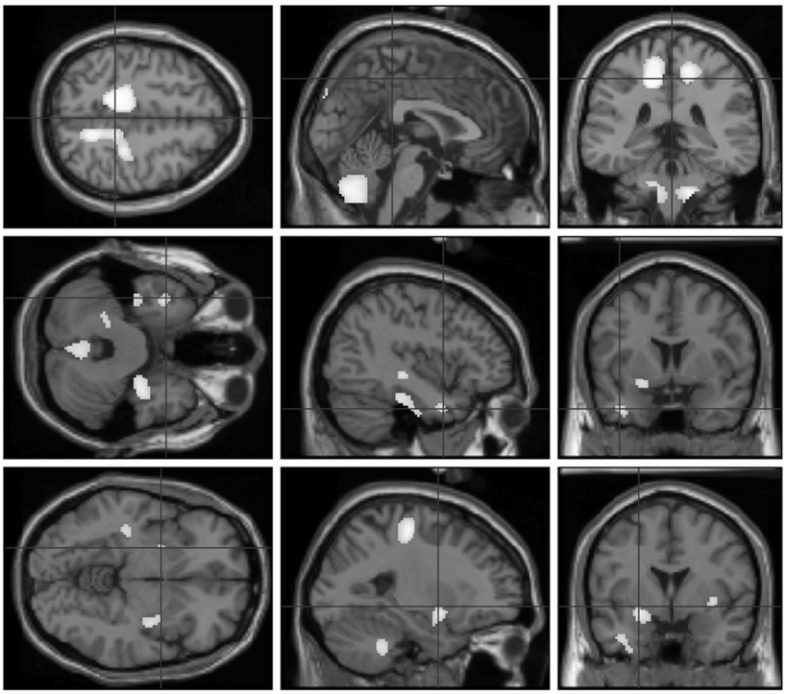

Fig. 3. Regions with significantly higher activity in long-term compared with recent-onset patients: primary motor, cerebellum inferior temporal and pallidum-putamen.

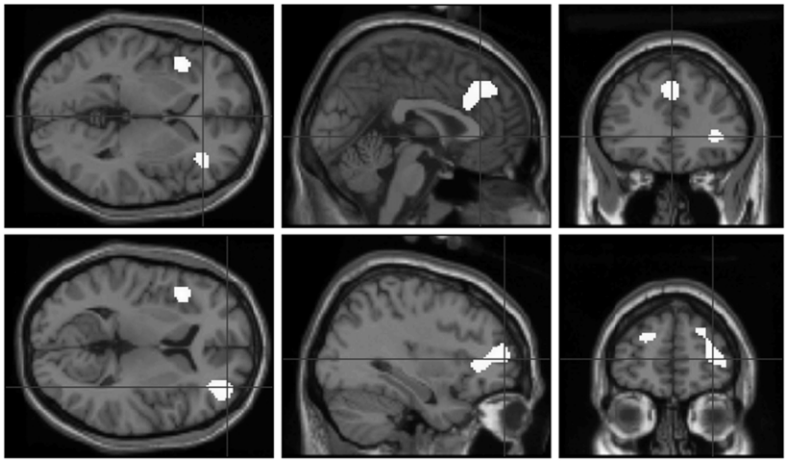

Fig. 4. Regions with significantly lower activity in long-term as compared with recent-onset patients: insula, anterior cingulate and dorsolateral prefrontal.

metabolic rate at this level in the LT patients. Such an increase is observed even on short-term treatment (Bartlett et al., 1994). The absence of higher activity in pallidum-putamen in our pooled group of patients compared with controls may be explained by the existence of decreased striatal activity in schizophrenia prior to treatment, as has been reported for neuroleptic-naive patients (Buchsbaum et al., 1992; Shihabuddin et al., 1998).

A higher activity in the inferior temporal region was found in the LT patients compared with the RO group. Previous studies (Vita et al., 1995; Andreasen et al., 1997) showed a reduction of metabolism in the temporal cortex of neuroleptic-naive patients with respect to controls, not replicated in neuroleptic-withdrawn cases (Vita et al., 1995). It is therefore unlikely that these metabolic changes were just a consequence of the schizophrenia. All these data together allow us to hypothesize a long-term effect of neuroleptics increasing temporal, cerebellar and motor cortex activity in schizophrenic patients.

4.2. Findings attributable to schizophrenia

Patients showed hypoactivity of the primary visual area. This finding is not likely to be an artifact due to somnolence induced by the haloperidol, since other studies in neuroleptic-naive patients have also described a similar hypoactivity in resting-condition PET scans (Andreasen et al., 1997), as well as hypometabolism in Brodmann area 19 in chronic patients (Kim et al., 2000). The absence of differences in the visual area between the LT and RO groups is another argument against a pharmacological origin of this finding. Moreover, Bartlett et al. (1994) did not detect visual hypoactivation in haloperidol-treated healthy controls. An explanation for this hypoactivation might come from the hypoactivity of the NMDA-type receptors for glutamate, a mechanism that has been previously related to schizophrenia (Olney et al., 1999; Tamminga, 1999). Administration of ketamine, an NMDA antagonist, produced hypoactivation of the primary visual area in schizophrenic patients (Lahti et al., 1995).

Compared with controls, patients in our study showed insular hypometabolism. This finding can be interpreted as an effect of the disease, as it is supported by previous evidence of insular volume reduction (Goldstein et al., 1999; Wright et al., 1999; Crespo-Facorro et al., 2000) and decreased insular activity during verbal generation tasks (Curtis et al., 1998). Decreased insular activity has also been reported in patients that showed higher error rates during a task involving suppression of reflexive saccadic eye movements and during the

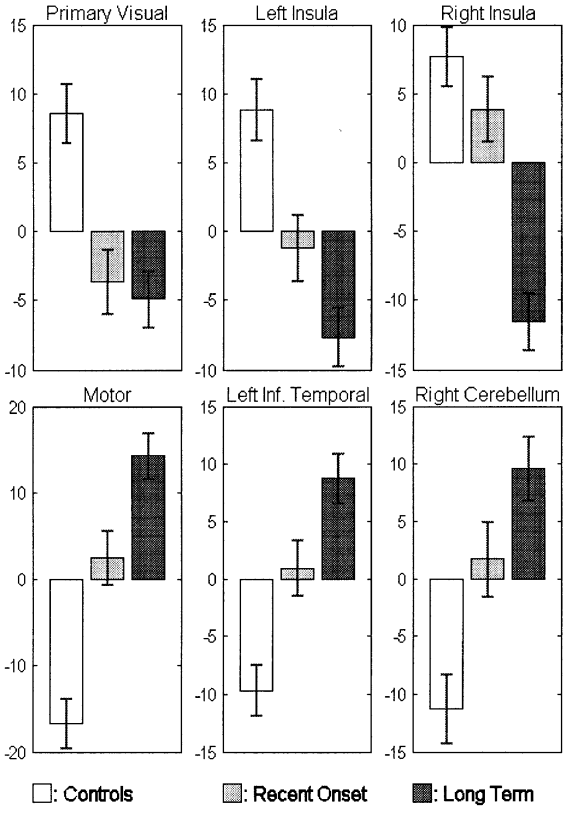

Fig. 5. Detailed description of the results of Table 2, showing the differences between controls and the two groups of schizophrenic patients. The bar graph shows the effect size (in % of global metabolism units) and 90% confidence interval for each comparison.

Wisconsin Card Sorting Test (Crawford et al., 1996). The possibility that the changes in insular metabolism were a secondary effect of the treatment cannot be totally ruled out, but there are some arguments against this hypothesis: previous studies on the effect of haloperidol did not show any selective decrease of insular activity (Bartlett et al., 1994; Holcomb et al., 1996), whereas insular hypometabolism was found in the resting condition in chronic schizophrenia after a neuroleptic washout longer than 3 weeks (Kim et al., 2000).

The thalamus sends excitatory projections to both the visual cortex and insula (Mufson and Mesulam, 1984). Thus, the thalamic defect described in schizophrenia (Pakkenberg, 1992; Andreasen et al., 1994; Buchsbaum et al., 1996), may also contribute to the decreased activation of structures expected to be metabolically active during the resting condition.

The comparison between LT and RO patients in our study also showed dorso-lateral prefrontal cortex hypometabolism in the former group, in agreement with the absence of resting hypofrontality in the initial stages of schizophrenia (Catafau et al., 1994). This difference between RO and LT patients might relate to the longer illness duration in the LT group, which may produce progressive frontal atrophy (Gur et al., 1998; Rapoport et al., 1999). An effect of chronic treatment could have also contributed to the lower frontal activity in LT patients (Holcomb et al., 1996), though Szechtman et al. (1988) did not find hypofrontality after 7.4 years of medication with classical neuroleptics. Besides, Berman et al. (1992) showed that higher cumulative exposure to neuroleptics in twins concordant for schizophrenia was not associated with hypofrontality.

We cannot discriminate if the hypoactivity in the cingulum of the LT patients is a chronic effect of schizophrenia, of the treatment, or both. Available evidence supports decreased activity (Tamminga et al., 1992; Ebmeier et al., 1995), lower *N*-acetyl-aspartate levels (Deicken et al., 1997) and reduced neuronal density (Benes, 1993) in this region in schizophrenia, although its activity has also been shown to decrease with haloperidol (Bartlett et al., 1994; Holcomb et al., 1996).

The difference in sex distribution between the LT and RO groups might have somehow distorted our results, considering the study of Gur et al. (1995) showing that normal males show higher activity in the cerebellum and lower activity in the cingulate. However, despite the fact that the LT group had a greater proportion of females, the metabolic changes were not in consonance with the results of Gur et al. (1995) Thus, it seems unlikely that our comparison between patient groups was affected by gender.

A possible limitation of our approach could be the use of a resting cognitive condition. Nevertheless, PET studies in non-resting conditions can also lead to a difficult interpretation of the changes since the use of tasks with a strong frontal com-

ponent that increases activity (Andreasen et al., 1992; Catafau et al., 1994; Miller et al., 1997) may interact with the decrease due to neuroleptics (Holcomb et al., 1996).

There are some important methodological concerns in the analysis of PET data using SPM techniques that may lead to discrepant results in the literature. A possible source of inaccuracies is the spatial normalization, since it is common practice to use the template provided with SPM (based on ^{15}O-water) to normalize FDG images. To date, it is not known to what extent this may alter the results. Other SPM processing parameters such as the type of intensity normalization or the degree of smoothing must be meticulously reported since they may also account for differences in the results.

Another important issue is the diversity of *P*-value thresholds accepted as significant in different studies. This problem relates to the multiple comparison problem in statistics, and has no universally accepted solution. Our approach has been to validate the particular *P*-value thresholds used throughout the study on the basis of bootstrapping techniques, therefore being more robust than any arbitrary selection, as it is done in most SPM studies. We have also labeled our findings according to evidence levels, in such a way that possible future comparisons with other works or meta-analysis should be easier.

In summary, our findings support the existence of a distinctive pattern of metabolic brain activity in the resting condition in schizophrenia characterized by a decreased activation of visual cortex in RO and LT patients, insular hypometabolism and a certain degree of hypofrontality in the LT group. Long-term administration of haloperidol increased cerebellar and motor area metabolism, and to a lesser extent, decreased frontal activity.

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