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ORIGINAL PAPER

Optimized voxel brain morphometry: association between brain volumes and the response to atypical antipsychotics

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Abstract To date, few studies have addressed the relationship between brain structure alterations and responses to atypical antipsychotics in schizophrenia. To this end, in this study, magnetic resonance imaging (MRI) and voxel-based morphometry (VBM) were used to assess the relationship between the brain volumes of gray (GM) and white (WM) matters and the clinical response to risperidone or olanzapine in 30 schizophrenia patients. In comparison with healthy controls, the patients in this study showed a bilateral decrease in the anteromedial cerebellar hemispheres, the rectal gyrus and the insula, together with bilateral increases in GM in the basal ganglia. Both patient groups had a significantly smaller volume of WM in a region encompassing the internal and external capsules as compared to the controls. We found an inverse association between striatal size and the degree of clinical improvement, and a direct association between the degree of insular volume deficit and its improvement. The non-responder patient group showed a significant decrease in their left rectal gyrus as compared with the responder group. This study reveals a pattern of structural alterations in schizophrenia associated with the response to risperidone or olanzapine.

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Introduction

Most studies addressing the relationship between brain structure alterations and response to antipsychotics have been performed using data from patients treated with classical drugs [35, 59] or clozapine [18, 33]. However, given the current patterns of treatment, it seems advisable to analyze possible relationships between such alterations and the response to newer antipsychotics. To date, few such studies are available; one group found that subsequent responders to risperidone had greater hippocampal volumes than patients who failed to respond to this drug [48]. In previous studies using methods based on the definition of regions of interest (ROIs), the authors reported no association between the cerebral structural data and the response to risperidone in initial episodes of schizophrenia [42], as well as a direct association between the degree of orbitofrontal atrophy and response to olanzapine [44].

Despite this, ROI-based studies may overlook the contributions to treatment response of regions not a priori included in the analyses. Comparison of whole-brain morphology using voxel-based morphometry (VBM) may help one to overcome this problem. In addition, this technique allows for the assessment of the relationship between white matter (WM) volumes and treatment response. To this end, in this study, optimized VBM was applied to compare the brain structures of patients, respectively, with good and poor responses to atypical antipsychotics in the medium term.

Based on the above, it was hypothesized that both groups would share anatomical differences with respect to

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healthy controls, attributable to illness and/or the treatment received previously, and that patients with a worse response would show greater anatomical deficits in regions of relevance to schizophrenia.

Subjects and methods

Subjects

Using magnetic resonance imaging (MRI), structural data from 30 chronic schizophrenia patients (14 males) and 31 healthy controls (18 males) were analyzed. None of these subjects had been included in any previous MRI report made by our group. In most cases, the patients had previously been treated with atypical antipsychotics (25 cases) or were neuroleptic-naïve (5 cases). They met the DSM-IV TR criteria for paranoid (24 cases) or undifferentiated (6 cases) schizophrenia. During the preceding year, the patients had received risperidone (20 cases, mean dose 4.9 ± 2.1 mg), olanzapine (10 cases, mean dose 9.8 ± 6.21 mg), quetiapine (6 cases, mean dose 491.7 ± 216.1 mg), amisulpride (4 cases, mean dose 228.3 ± 85.1 mg), clozapine (4 cases mean dose 237.1 ± 136.3 mg), and ziprasidone (2 cases, mean dose 122.3 ± 47.7 mg). Sixteen patients received more than one antipsychotic. Cumulative lifetime exposure to antipsychotic treatment was assessed for each case based on clinical records and information from the patients and their families (Table 1).

The patients were admitted to the psychiatric unit of our hospital due to a psychotic crisis, in most cases temporally related to medication incompliance. Twenty-two of the patients had abandoned their medication for a period longer than 2 weeks and shorter than 3 months, according to the available information gathered in clinical interviews with the patients and their families. After inclusion, all the patients were switched to risperidone or olanzapine, the choice being made on a clinical basis. During their stay in hospital, 20 patients were prescribed monotherapy with risperidone (mean dose 5.3 mg/d, sd 2.6), and 10 patients received monotherapy with olanzapine (mean dose 17.8 mg/d, sd 4.9). These drugs show an adequate benefit-risk ratio for the treatment of patients with schizophrenia with a similar profile to that of the patients included in this study [27].

The MRI scan was acquired within the initial week of that stay, without any specific wash-out period. Clinical response to risperidone or olanzapine was assessed prospectively after the MRI acquisition. The patients were monitored for a minimum of 1 year after discharge, with at least one visit every month. Although assessment of the relationship between cerebral structure and clinical response was dimensional (i.e., correlative), it was also considered to be of interest to compare the specific structures between the patients categorized clinically as responders or non-responders. Accordingly, the information available regarding the acute response to treatment and outcome during that 1-year follow-up period was used to categorize two groups at the end of the period as follows.

To be qualified as responders, the patients had to show a good response in the short-term (i.e., during the first 3 weeks of treatment), defined as a reduction in their total Positive and Negative Symptoms Scale (PANSS) scores equal to or greater than 35%, as well as a Clinical Global Impression (CGI) score of 3 or lower at the end of that period. In addition, they could not have been readmitted to any psychiatric unit during the whole follow-up period, and their CGI had to remain equal to or less than 3 during that period. Twenty patients met these criteria, including three neuroleptic-naïve(NN) patients; 10 were men and 10 were women. Thus, non-responder patients ($n = 10$, including 2 NN patients; 4 females, and 6 males) showed a reduction of lower than 35% in their total PANSS scores and underwent one or more relapses that required readmission to the unit

Table 1 Clinical and demographic characteristics of the patient groups

	Patients ($n = 30$)	Non-responder ($n = 10$)	Responder ($N = 20$)	Controls ($N = 31$)
Age (year)	34.1 (10.6)	39.6 (10.3)	31.0 (9.8)	36.83 (12.19)
M:F ratio	16:14	6:4	10:10	18:13
Illness duration (year)	13.4 (5.9)	15.5 (5.4)	11.2 (6.1)	
Cumulative NL exposure (gr)	1,411.2 (728.1)	1,389.1 (871.9)	1,491.5 (675.2)	
PANSS positive	28.3 (5.1)	29.2 (5.8)	27.8 (4.8)	
PANSS negative	24.1 (6.7)	27.7 (6.8)	21.7 (5.6)	
PANSS total	97.3 (16.5)	102.6 (16.3)	89.9 (12.6)	
Change PANSS-P (%)		32.1 (13.4)	61.4 (14.8)	
Change PANSS-N (%)		7.4 (3.4)	28.2 (13.9)	
Change PANSS-T (%)		21.5 (17.6)	44.2 (20.3)	

The PANSS change represents the percentage decrease from the baseline to after-treatment conditions

during the follow-up period. The CGI score in that group remained equal to or higher than 4 after discharge. The change in the PANSS score after 3 weeks of treatment can be considered as an acute response criterion, while the categorical response versus no response after 1 year can be considered as a clinical stability criterion (also taking into account the acute response).

Regarding the treatment received during the follow up, 14 responders received risperidone and six received olanzapine during the follow-up period. After relapse, the non-responders were switched to other treatments for clinical reasons if needed.

Compliance with treatment was monitored by daily clinical interviews held during the initial study period (3 weeks), taking into account the clinical examination (psychiatric status and side effects) and information collected from the patients, nursing staff, and relatives. In all cases, according to these sources of information, compliance was deemed to have been good during that period. During the rest of the follow-up period, compliance was assessed similarly, but on a monthly basis.

The exclusion criteria included a history of any neurological illness or MRI findings judged clinically relevant by a radiologist blind to the diagnosis: cranial trauma with loss of consciousness; past or present substance abuse—except nicotine or caffeine; the presence of any other psychiatric process or treatment, and treatment with drugs known to act on the central nervous system. A urine analysis was used to rule out current substance abuse.

Written informed consent was obtained from the patients and their families. The research board endorsed the study.

Imaging methods

MRI acquisition

MR imaging was performed with a Philips Gyroscan 1.5T scanner. For each subject, a 3D T1 acquisition was obtained with the following parameters:
TR = 7.5 ms, TE = 3.5 ms, Flip angle: 8°, 0.78 × 0.78, FOV = 240 mm × 240 mm, matrix size = 256 × 256, 150 slices (thickness 1 mm^3).

All scans in the patients and control groups were acquired in the same system with the same protocol. The VBM procedure transforms the resolution to the standard MNI (Montreal Neurological Institute) brain in the Talairach coordinates system.

Image processing

The T1-weighted MRI scans were recorded using a diffeomorphic image registration algorithm, DARTEL-based VBM [5], implemented using SPM8 software in the MATLAB 7.6/R2008a environment. DARTEL (Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra) (Ashburner, 2007) is a SPM 8 toolbox. This algorithm records inter-subject images using diffeomorphisms, which preserve the object properties through deformations, twistings, and stretchings. To record the images, a template is generated using images from control subjects, and each patient image is deformed to the template using diffeomorphisms.

Using DARTEL, gray matter (GM) and WM differences between patients and controls were assessed at voxel level. Age, sex, education, and total intracranial volume were included in the model as nuisance variables. The level of significance was set at a voxel level of $P \leq 0.001$ (uncorrected) and a cluster level of $k_E \geq 200$ voxels for whole brain analysis. A confirmatory analysis corrected for multiple comparisons (Family-Wise Error (FWE, $P < 0.05$) was also performed.

The significant GM and WM differences found in the above comparison between patients and controls were used as a mask within which correlations with clinical changes were sought. The significance of the association between GM and WM distribution within that mask was assessed, and the percentage of change in the total PANSS scores in the patients taken jointly. These analyses included the same nuisance variables as the comparison between the patients and controls, in addition to the basal total PANSS scores of each patient. As in the other comparison, the level of significance was set at $P < 0.001$ uncorrected ($k_E \geq 200$ voxels), and FWE confirmatory analyses were performed.

Finally, with the same methodology, the GM and WM volumes between patients qualified as responders and non-responders were compared. The relationship between the estimated exposure to neuroleptics and brain structure in the whole group of patients was tested (Pearson's r).

The output for each comparison was a statistical parametric map that revealed the location of gray matter abnormalities in the brain. These areas were superimposed over a T1-weighted template. The spatial locations of the abnormal brain regions were detailed with Talairach coordinates.

Results

There were no significant differences in age, sex distribution, or parental socioeconomic level between groups (Table 1). Nor were illness duration, the duration of treatment, cumulative antipsychotic exposure, or type of treatment after follow up significantly different between patient groups (Table 1).

Structural differences between groups

Gray matter differences

As compared to the healthy controls ($P < 0.001$ uncorrected, $k_E \geq 200$ voxels), the patients were seen to have a decrease in GM in the anteromedial cerebellar hemispheres (Fig. 1), the insula (Brodmann area (BA) 13), and the rectal gyrus (BA 11). Moreover, both groups of patients showed bilateral increases in GM in the dorsal putamen and pallidum (Fig. 2) with respect to the healthy controls.

After FWE correction, the patients still showed a significant GM decrease in the anterior cerebellum and the rectal gyrus and a significant GM increase in the putamen ($P < 0.05$).

No statistically significant association was seen between cumulative drug exposure and GM distribution in the Sz patients (Table 2).

White matter differences

In comparison with the healthy controls, the patients had a significantly smaller WM volume in an extended region encompassing the internal and external capsules as well in the medial temporal region (Fig. 3). This difference persisted even after FWE correction.

Correlation with changes in PANSS scores

Gray matter

In the patients, the percentage of change in the total PANSS score after 3 weeks of treatment with risperidone or olanzapine was inversely related to the right caudate and left putamen volumes (i.e., the PANSS scores of patients with greater caudate and putamen volumes were less likely to decrease). Similarly, the bilateral insula (BA 13) GM volumes were

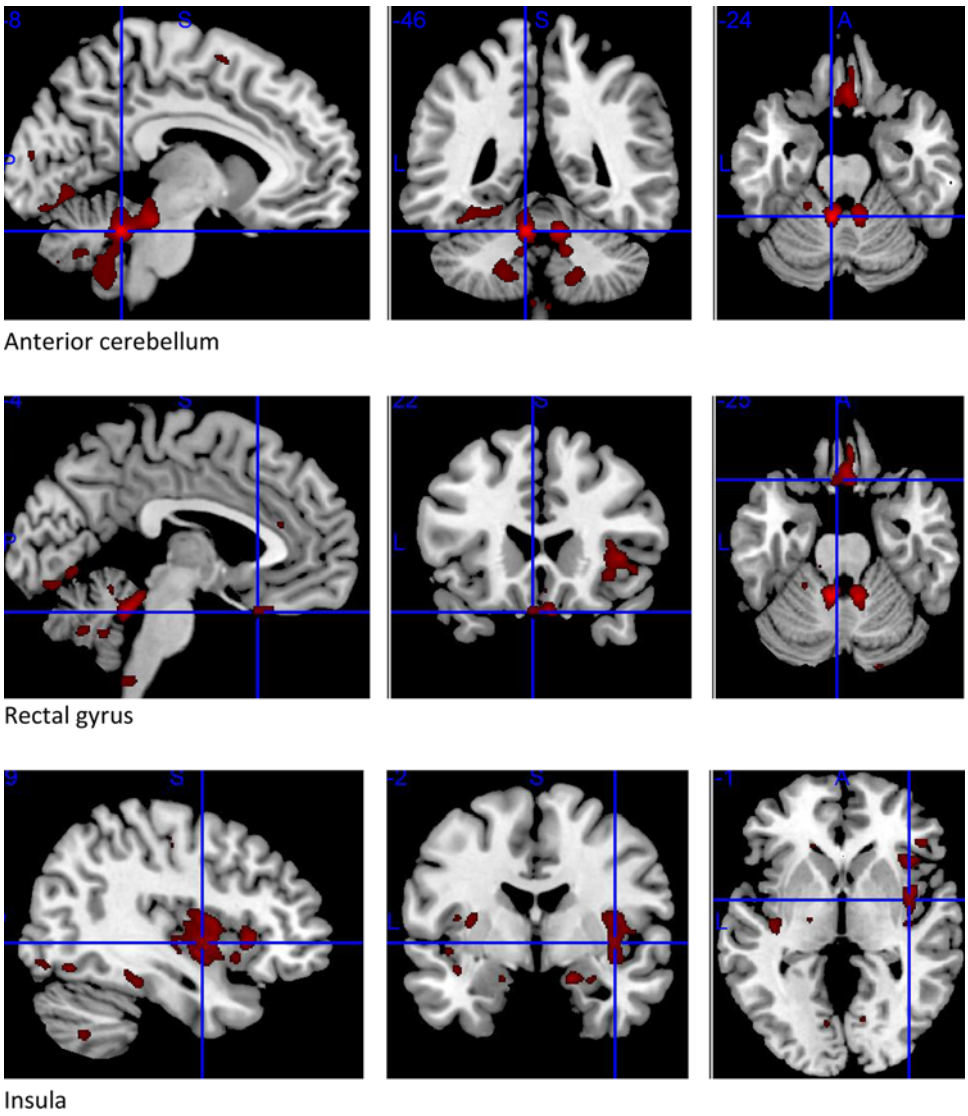

Fig. 1 Significant GM reductions in patients as compared to healthy controls ($P < 0.001$, uncorrected, $K_E > 200$ voxels)

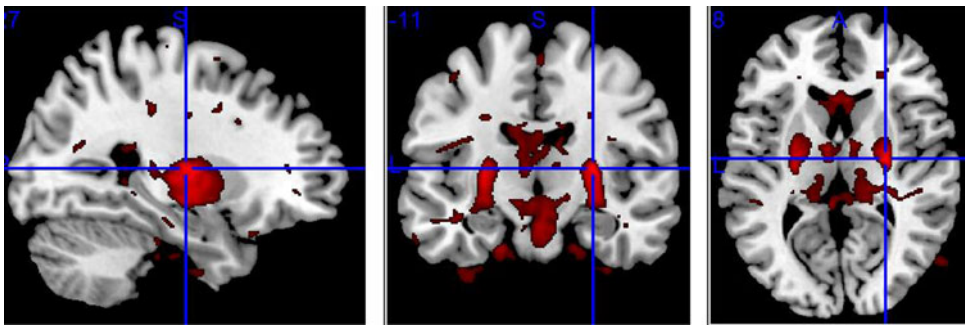

Fig. 2 Areas of significant GM increase in patients as compared to healthy controls ($P < 0.001$, uncorrected, $K_E > 200$ voxels)

Table 2 Location, peak coordinates, and voxel extension of the volume differences between groups, and correlations between cerebral volumes and clinical change ($P < 0.001$, uncorrected in all cases; $k_E > 200$)

Comparison	Region	Peak coordinates	K_E (voxel extension)
GM reductions in patients as compared to healthy controls	Anterior cerebellar lobe, lingual gray matter (bilateral)*	(−8, −46, −18)	23,027
	Insula (bilateral)	(−39, −2, −1)	392
	Claustrum (bilateral)	(−34, −8, 8)	593
	Rectal gyrus (bilateral)*	(−4, 20, −22)	1,055
GM increase in patients as compared to controls	Putamen (bilateral)*	(27, −10, 8)	54,859
WM decrease in patients	Internal and external capsules and parahippocampal WM*	(26, −10, 3) (−2, 27, 0)	52,783
Inverse association between regional GM volume and change in total PANSS scores	Insula (bilateral)	(−34, 3, 3)	286
	Putamen (bilateral)*	(27, −8, 7)	3,020
GM reductions in non-responder as compared to responder patients	Left rectal gyrus	(−3, 32,−18)	384

WM white matter, *GM* gray matter

* Differences still significant after FWE correction ($P < 0.05$)

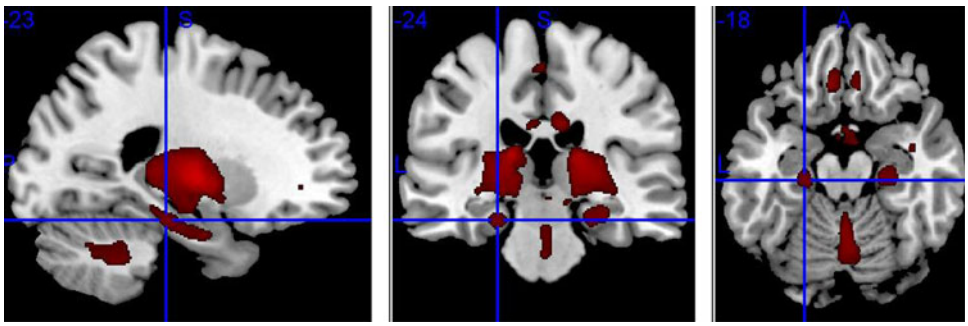

Fig. 3 Areas of significant WM decrease in patients as compared to healthy controls ($P < 0.001$ uncorrected, $K_E > 200$ voxels)

inversely related to changes in the total PANSS scores (the clinical scores of patients with more GM in these regions at the baseline were less likely be reduced after treatment; Fig. 4).

White matter

No significant relationships were found between WM volumes and PANSS changes.

Differences between responder and non-responder patients

Comparison of the responder and non-responder patients revealed a significant decrease ($P < 0.001$, uncorrected) in rectal gyrus GM in the latter (Fig. 5).

Discussion

It was found in this study a different pattern of brain abnormalities associated with the medium-term outcome of treatment with atypical antipsychotics in schizophrenia patients. In comparison to controls, patients showed a decrease in cerebellar and insular and rectal gyrus GM, a decrease in WM, and an increase in basal ganglia (BG). Increases in BG and deficits in the insula were associated with a better acute response to treatment. The patients with a poorer response in the medium term showed additional decreases in the rectal gyrus.

The observed increases in dorsal BG volumes (pallidum and putamen) in our patients can be attributed to previous

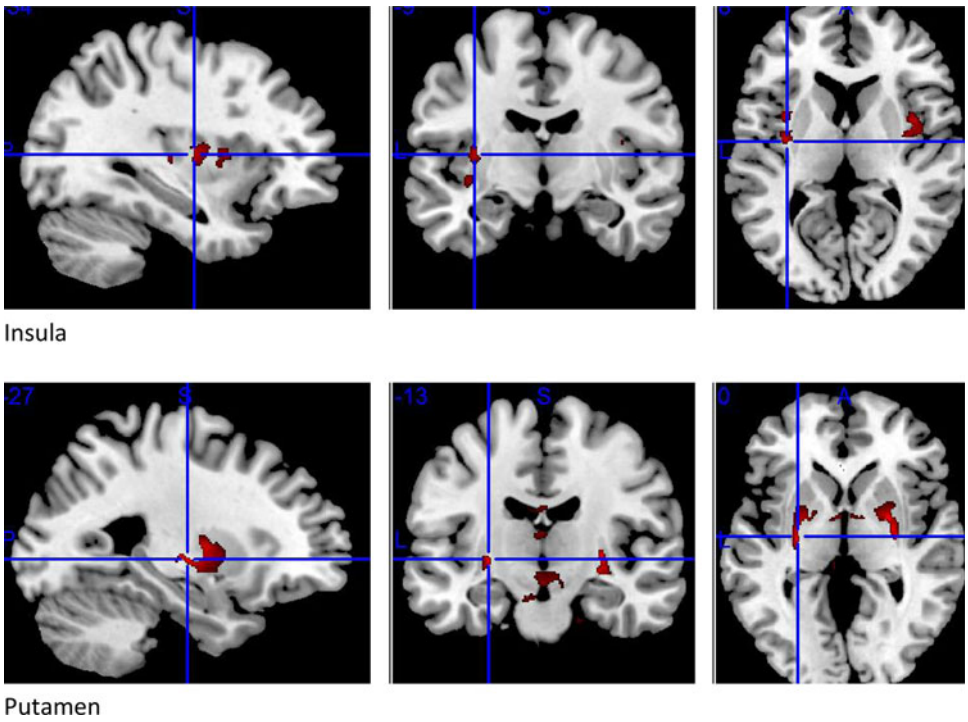

Fig. 4 Areas with an inverse significant ($P < 0.001$, uncorrected, $K_E > 200$ voxels) association between regional GM volume and improvement in total PANSS scores

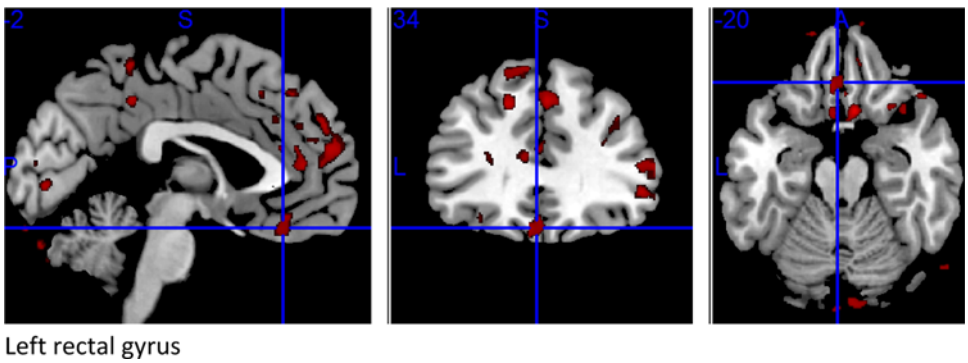

Fig. 5 Areas of significant GM decrease in resistant as compared to non-resistant patients ($P < 0.001$, uncorrected)

treatment. Treatment with typical antipsychotics increases BG volume [7, 11, 14, 15, 52, 57], and this—according to the results of this study—may also occur in patients who have only received atypicals. Since most of our patients had received risperidone along the previous year, that drug might have increased their BG volumes. This would be coherent with the increase in the putaminal volume reported for risperidone [20], although in another report [32], the change in GM at the same level after 1 year with risperidone was not significant. Along the same line, clozapine increases caudate volumes in animals [2].

In the patients under this study, there was an inverse association between increases in BG volume and clinical improvement. This is coherent with the larger right caudate volume reported for the deficit syndrome in schizophrenia [8], since patients with this syndrome are less likely to benefit from antipsychotics [1]. However, an association between larger BG and less clinical improvement seems discordant with previous data, since schizophrenia patients with a poor response in the long term have been shown to have smaller striatal volumes [10, 38], regardless of the type of previous treatment (i.e., typical or atypical) [10]. Moreover, in a completely different sample, the authors have previously reported smaller striatal volumes (caudate and putamen) in poor outcome, treatment-resistant schizophrenia patients in the long-term in comparison to less severe patients, both having received treatment with typical antipsychotics [41]. In the same vein, a higher rate of reduction of putamen volumes was described in poor-outcome as compared with good-outcome schizophrenia patients after 4 years of follow up [39].

There is no clear explanation for this apparent paradox, although it could be speculated that putamen volumes may be related to the acute response to antipsychotics, which

would be reflected in decreases the PANSS scores in our patients, perhaps through its association with available dopamine D2 receptors. In addition, a stable reduction of caudate volume could confer a worse prognosis in the long term, which would not be reflected in the correlation between PANSS changes after 3 weeks of treatment and brain volumes. It could be also speculated that the association between greater putaminal size and poorer acute response may be related to the reduced plasticity of the BG region in response to treatment. A reduction in striatal size is expected after the interruption of treatment [49]. Since our patients had abandoned their treatment, it is possible that the striatal size of the poor-outcome patients may have not been decreased, suggesting reduced plasticity in that region. In agreement with this possibility, the smaller striatum in poor-outcome patients [10, 38] may be related to the absence of an increase in size in response to the initial antipsychotic treatment.

The patients showed a decrease in cerebellar volume with respect to the healthy controls, which suggests an alteration in this region due to schizophrenia, which receives support from structural [45], functional [13], and histological [53] studies. Some authors have reported an anatomical anterior cerebellar deficit similar to that found by us [45], while others have reported more posterior deficits [47]. A role for this deficit in cerebellar volume has been proposed in cognitive alteration in schizophrenia [3], and cerebellar alterations in this illness have also been shown to correlate with the duration of negative and positive symptoms, and with psychosocial impairment [54]. Neurological cerebellar signs in neuroleptic-naïve patients are associated with a poorer premorbid adjustment and more negative symptoms [24]. A recent review has stressed the regulatory role that the cerebellum may play in cortical activity and its possible consequences for schizophrenia [4]. However, according to the results of this study, cerebellar deviations do not have a strong influence on the subsequent response to antipsychotics.

Insular decreases have frequently been reported in schizophrenia [12, 17, 19, 21, 25, 30, 38, 56], in particular in its anterior portion [36, 51], and in chronic rather than in FE patients [38, 51]. Such a decrease has been found to be specific to schizophrenia [26, 37]. In the same vein, the volume of the orbitofrontal area has repeatedly been shown to be decreased [6, 9, 22, 28], as was the case of in the studied patients. Interestingly, the reduction in volume of that region has been shown to be related to prepulse inhibition deficits [31], the severity of negative symptoms [6], or cognitive alterations [50] in schizophrenia patients.

The patients also showed a reduction in WM in the internal and external capsules, possibly indicating a reduced cortico-subcortical connectivity associated with that illness, since this region contains a major WM tract providing reciprocal connections between the frontal cortex, striatum, and thalamus. Such a reduction in WM is consistent with previous findings [16], [55], [58], suggesting a focal deficit in patients with schizophrenia. Of particular interest is that a WM reduction in the internal capsule has been reported during the initial year of illness in first-episode schizophrenia patients, this reduction being related to the clinical outcome [55]. Although such size differences do not indicate, per se, a functional abnormality, a relationship between size and alterations to connectivity is suggested by the association in the same group of smaller callosal size and lower average anisotropy [40]. Reduced anisotropy has also been found in the internal capsule in schizophrenia [46].

Contrary to our hypothesis, there was an inverse correlation between insular GM volumes with the decrease in PANSS scores. Although this may represent a type I error, there are other reports showing an inverse association between regional GM volumes and responses to atypical drugs [33, 43]. In particular, in an entirely different sample, the authors have previously reported that patients with less orbitofrontal GM respond better to olanzapine [44]. Moreover, in another completely different sample, it was found that clozapine response was inversely related to intracranial and hippocampal volumes [43]. Previously, another group has reported a direct association between "prefrontal sulcal prominence" (a measure of frontal GM atrophy) and the response to clozapine [18]. Furthermore, a direct association was observed between insular volume and bizarre behavior scores in a sample with a significant insular decrease [36], indicating that clinical severity may be higher in some patients with fewer GM deficits. Nevertheless, there are also reports showing that patients with more marked GM deficits may show a poorer response to clozapine [18, 43] and classical antipsychotics [23, 29, 34]. These discrepant results indicate the need for further studies addressing this important topic. One possible interpretation for such discrepancies is that some alterations, such as the insular reduction or striatal increase in our patients, may be linked to the response to treatment in the short term, while other structural changes, such as the latter cortical deficits, may in turn be related to long-term outcomes. This could explain the more severe deficits in our non-responder patients, albeit only in the orbitofrontal cortex, since our response criteria assessed the outcome after 1 year of follow up. Despite this, one cannot be sure if the greater reduction in this region is a prognostic marker independent of the action of antipsychotics. Thus, the observation of its reduction in non-responders should be considered preliminary.

Our study has its limitations. The first is due to the different treatments received by the patients in the follow up. Despite this, olanzapine and risperidone are standard

treatments with no significant differences in their rate of response. Moreover, the history of previous treatments differed among the patients, although this does not diminish the interest of the relationship observed in this study between baseline structural alterations and prospective treatment response. The patients had been treated over the previous years, but this is a typical clinical situation, and it would be useful to have prognostic methods available at our disposal to assess the likelihood of response to these treatments. The quantitative exposure to antipsychotics was similar between the groups, decreasing the likelihood that previous treatment might have been the only reason behind the differences observed. In any case, follow-up studies in neuroleptic-naïve patients would be needed to address the hypothesis of an association between structural cerebral variation and clinical response to antipsychotics. The sex distribution was different between responder and non-responder patients, although this does not influence the correlations between PANSS changes and brain structure calculated for the patients considered jointly.

In conclusion, the study data show that brain anatomy may be related to the clinical response to atypical antipsychotics. Taken together, our data lend additional support to the existence of different cerebral abnormalities within the diagnosis of schizophrenia, some of them associated with a poorer response to new antipsychotics in chronic patients.

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