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Patterns of Structural MRI Abnormalities in Deficit and Nondeficit Schizophrenia

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Negative symptoms of schizophrenia have generally been found in association with ventricular enlargement and prefrontal abnormalities. These relationships, however, have not been observed consistently, most probably because negative symptoms are heterogeneous and result from different pathophysiological mechanisms. The concept of deficit schizophrenia (DS) was introduced by Carpenter et al to identify a clinically homogeneous subgroup of patients characterized by the presence of primary and enduring negative symptoms. Findings of brain structural abnormalities reported by magnetic resonance imaging (MRI) studies focusing on DS have been mixed. The present study included 34 patients with DS, 32 with nondeficit schizophrenia (NDS), and 31 healthy comparison subjects, providing the largest set of MRI findings in DS published so far. The Schedule for the Deficit Syndrome was used to categorize patients as DS or NDS patients. The 2 patient groups were matched on age and gender and did not differ on clinical variables, except for higher scores on the negative dimension and more impaired interpersonal relationships in DS than in NDS subjects. Lateral ventricles were larger in NDS than in control subjects but were not enlarged in patients with DS. The cingulate gyri volume was smaller in NDS but not in DS patients as compared with healthy subjects. Both groups had smaller dorsolateral prefrontal cortex and temporal lobes than healthy subjects, but DS patients had significantly less right temporal lobe volume as compared with NDS patients. These findings do not support the hypothesis that DS is the extreme end of a severity continuum within schizophrenia.

Key words: primary negative symptoms/lateral ventricles/temporal lobes/dorsolateral prefrontal cortex/cingulate gyri

Introduction

The concept of deficit schizophrenia (DS) was introduced by Carpenter et al[1] to identify a clinically homogeneous subgroup of patients characterized by the presence of primary and enduring negative symptoms. Subjects with DS, relative to those with nondeficit schizophrenia (NDS), have poorer premorbid adjustment[2–4]; more impaired general cognitive abilities,[5–7] social cognition,[7] and frontoparietal functioning[5,6,8]; different electrophysiological abnormalities[9]; an excess of summer birth[10–13]; a more frequently insidious onset of illness[3]; a similar severity of productive symptoms; a lower severity of dysphoria[14]; a more frequent resistance to antipsychotic treatment[15]; a worse long-term outcome; and a more frequent family history of schizophrenia.[16–19] A high degree of stability and a good test-retest and interrater reliability have been reported for the deficit/nondeficit categorization.[3,16,20]

Based on previous studies on brain structural correlates of negative symptoms,[21–29] more enlarged ventricles and smaller prefrontal volumes might be expected in patients with DS as compared with those with NDS. However, the evidence produced by magnetic resonance imaging (MRI) studies focusing on DS has been mixed. Buchanan et al[30] investigated 17 patients with DS, 24 with NDS, and 30 healthy comparison subjects by structural MRI and, unexpectedly, found that the patients with NDS had significantly smaller right and left prefrontal volumes than those with DS; with respect to controls, patients with DS did not differ on prefrontal measures, while those with NDS had smaller total right and left prefrontal volumes. Both patient subgroups had larger left caudate volumes and smaller right and left amygdala/hippocampus complex than controls; a trend toward a larger right caudate volume was observed in DS patients only. Gur et al[31] found no ventricular enlargement in DS vs NDS patients. Turetsky et al[32] studied 21 patients with

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DS and 49 with NDS and found abnormal temporal lobe asymmetry only in patients with DS, in which a selective increase in left temporal lobe cerebrospinal fluid (CSF) volume was observed in comparison with both NDS patients and healthy controls. Sigmundsson et al,[33] using dual echo MRI in a group of 27 patients with primary and enduring negative symptoms and 27 healthy comparison subjects, found significant deficit of gray matter (GM) volume in the patient group at 3 main locations: (1) the left superior temporal gyrus and insular cortex, (2) the left temporal medial lobe (including hippocampus and parahippocampus), and (3) the anterior cingulate and medial frontal gyri. White matter (WM) deficits were found in similar locations of the left temporal lobe and extended in the left frontal lobe. The patient group also showed a relative excess of GM in the basal ganglia (putamen, globus pallidus). No difference was found in this study for the CSF, and no difference was reported for the lateral ventricles. Patients with schizophrenia without deficit features were not assessed in this study.

Differences in methods used to select patients may account for inconsistencies in findings. In fact, while in the study of Buchanan et al[30] the Schedule for the Deficit Syndrome[34] (SDS) was used to establish the diagnosis of either DS or NDS, in the studies by Gur et al[31] and Turetsky et al[32] patients were diagnosed according to the criteria proposed by Carpenter et al[1] but not according to the operational criteria provided by the SDS; in the study by Sigmundsson et al[33] the SDS criteria were used for the diagnosis, though it is not clear whether an interview to patients or relatives based on the schedule was used, and patients with NDS were not included, preventing direct comparison with the other studies.

The present structural MRI study, carried out as part of a large Italian multicenter study on DS and NDS,[6] provides the largest set of MRI findings in DS patients published so far. In the light of previously reported findings in subjects with DS or primary and enduring negative symptoms, the lateral ventricles, dorsolateral prefrontal cortex (DLPFC), cingulate gyri, temporal lobes, hippocampi, caudate nuclei, putamen, and globus pallidi were evaluated.

Methods

Subjects and Recruitment Procedures

The study was part of a large multicenter study carried out in patients who were regularly attending the outpatient units, day care programs, and rehabilitation centers of the University Psychiatric Departments of Naples, Milan, L'Aquila, and Pisa. For inclusion in the study, patients had to meet the following inclusion criteria: (1) a *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*), diagnosis of schizophrenia, confirmed by the Structured Clinical Interview for *DSM-IV* (SCID-I); (2) an age between 16 and 55 years; (3) no history of severe mental retardation, alcoholism, or drug abuse or dependence in the last 12 months, and no previous electroconvulsive therapy; (4) no significant changes in the clinical state or in drug treatment during the preceding 3 months; and (5) willingness to participate in the study procedures, expressed by providing written informed consent after complete description of the study. Patients meeting these criteria were then classified as having either DS or NDS after being interviewed with the SDS.[34] Information concerning translation, training, and interrater reliability for the SDS was reported elsewhere.[6] All subjects with DS, according to the SDS, were enrolled in the study. For each recruited patient with DS, an age- and sex-matched patient with NDS was recruited. Thus, 60 deficit and 60 nondeficit patients were recruited. Historical, clinical, and neuropsychological findings from the study were reported elsewhere.[6] MRI data were available for sixty-six of them: 34 with a diagnosis of DS (25 males, 9 females, age range 20–51 years) and 32 with a diagnosis of NDS (26 males, 6 females, age range 19–54 years). Eighteen patients did not give their consent to participate in the MRI procedures; 13 did not cooperate adequately with the MRI acquisition procedures; 14 were lost to MRI data analysis procedures due to data format incompatibility; and 9 were excluded for detectable motion artifacts. Patients included in MRI analyses were comparable to the whole group on demographic and clinical variables. Thirty-one healthy subjects were also recruited (21 males and 10 females, age range 18–50 years) for comparison on MRI measures. They were comparable to patients for age, gender, and education and had no personal or family history of major psychiatric disorders—as ascertained by the SCID-Non Patient and the Family History Questionnaire and Relative Psychiatric History Questionnaire—and no history of severe head trauma or substance-related disorders.

The study was approved by the local ethical committees of all centers and was carried out in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. A written informed consent to participate in the study procedures was obtained from all subjects.

Clinical Evaluation

The psychopathological evaluation included the Expanded Brief Psychiatric Rating Scale[35] (EBPRS), version 4.0; the Scale for the Assessment of Positive Symptoms[36](SAPS); and the Scale for the Assessment of Negative Symptoms[37] (SANS). The Strauss-Carpenter Scale[38] was used to assess patients' outcome on the 4 subscales "hospitalization", "work", "social relationships," and "symptoms."

MRI Protocol

A meeting of researchers from the different sites was organized before starting recruitment. At least one researcher from each site attended the meeting to discuss with the neuroradiologist (A.B.) from the central reference site (Biostructure and Bioimaging Institute, CNR and Diagnostic Imaging, University Federico II) the most appropriate sequence for each scanner to ensure the highest comparability among sites. In case further information was needed, the manufacturer was contacted to obtain the best possible match.

MRI protocol included 2 interleaved sets of 15 slices covering the entire brain obtained at 1.5 T on 4 different scanners (2 Magnetom Siemens, Erlangen—Germany, and 2 Signa GE, Milwaukee, WI), sampling the brain at a total of 30 levels. Each of the 2 sets was composed of 2 conventional spin-echo sequences, generating T1w and PD/T2w images (25 cm FOV, 256 × 256 acquisition matrix, 4-mm thick axial slices). The same TE was used for PD and T1w (either 15 or 30 ms, depending on scanner capabilities), while for T2w images it was 90. TR was 600 ms for T1w images and 2200–2300 ms for PD/T2w images.

Each site was requested to send sample images to the central reference site to ensure that the specified imaging sequence could be correctly executed and to verify the compatibility between the format used to save data on disk and the automated segmentation procedure.

MR Images Segmentation

The segmentation process was carried out at the central reference site. Segmentation of MR brain images into GM, WM, and CSF was obtained using a fully automated multispectral segmentation method.[39,40] This method provides, starting from a set of axial T1w-, T2w-, and PD-weighted conventional spin-echo images, a corresponding set of relaxation rate maps. The only constraint required by the algorithm is that a triplet of images (T1w, PD, and T2w) is available for each level. The same positioning parameters were thus used for T1w and PD/T2w image sets in each study. Segmentation was performed binarily, ie, each intracranial pixel was labeled as belonging univocally to GM, WM, or CSF.

Analysis of MR Images

The obtained MR images were exported onto a workstation Spark 20 and processed using an in-house routine, written using Interactive Data Language (Research Systems, Inc, Boulder, CO), which provides the volumes of selected structures of interest by applying the Talairach grid[41] to the segmented brain, as described in Quarantelli et al.[42]

Briefly, the software allows to interactively select the coordinates of the anterior and posterior commissure, thus defining the bicommissural line for each subject. Subsequent processing is fully automated: the software defines the box encompassing the whole brain, which is composed of 1056 smaller boxes, each assigned to 6 couples of structures (frontal, parietal, occipital, and temporal lobes; cerebellar hemispheres; and lateral ventricles) based on the labeling of cortical structures reported in the original atlas.[41]

Further details on the validated methods for regional automated measures of cerebral lobes and cerebral ventricles can be found in Quarantelli et al.[42]

For the purpose of the present work, the definition of cerebral lobes was integrated adding a separate labeling for the boxes belonging to the hippocampi (defined as the sum of amygdala, hippocampus and parahippocampal gyrus), cingulate gyri and DLPFC (defined as the sum of Brodmann areas 9,10,45 and 46), as reported in the original atlas.

Additionally, on each study, one neuroradiologist (M.Q.) and one properly trained psychiatrist (U.V.) traced manually bilaterally the caudate nuclei, putamen, and globus pallidus.

For each subject, regional measures of GM and CSF and of each structure of interest were divided by total intracranial volume (ICV, calculated from segmented maps as the sum of GM, WM, and CSF), thus providing fractional results calculated as percentage of the ICV. Investigators were blind to subjects' diagnosis.

Statistical Analysis

Data distributions were examined for normality and homogeneity of variance. In cases in which these assumptions were violated, common procedures for data normalization were adopted, starting from the exclusion of outlier measures, defined as those exceeding either 75th or 25th percentile by 1.5 times the interquartile range, in each group. In table 1, the number of outlier measures for each subgroup and structure is reported. These measures were replaced by the mean of the corresponding diagnostic subgroup. However, statistical analyses were also carried out retaining the original outlier values to assess the influence of their replacement on group differences.

Categorical variables were analyzed by the chi-square test. For continuous variables, in order to deal with the problem of multiple comparisons, the following strategies were adopted. First, for each investigated area, the lowest possible number of indices was included, according to criteria defined a priori on the basis of data reduction methods reported in the relevant literature. Second, analyses of variance (ANOVAs) were performed, with multivariate or repeated measures designs used when deemed appropriate. Third, the Huynh-Feldt correction for multiple comparisons was used when needed. Fourth, Tukey's Honest Significant Difference (HSD) procedure for unequal group size was used for post hoc comparisons only when a significant main effect or interaction had been found in the multivariate test. Measures from the SANS and SAPS were grouped into 3 dimensions[43–46]:

Table 1. Number of Outlier Measures in Each Group, for Each Structure

Area	Patients With DS (N = 34)		Patients With NDS (N = 32)		HCS (N = 31)	
	<25th Percentile	>75th Percentile	<25th Percentile	>75th Percentile	<25th Percentile	>75th Percentile
Right lateral ventricle		1		1		1
Left lateral ventricle		1		1		
Right dorsolateral prefrontal cortex					3	
Left dorsolateral prefrontal cortex						1
Right hippocampus				1		1
Left hippocampus			1		1	
Right cingulate cortex	3	1			1	1
Left cingulate cortex				1	1	1
Right temporal lobe			1			
Left temporal lobe	3					
Right putamen	1	1	1	1	2	2
Left putamen	2		2			
Right pallidum	1		1			
Left pallidum	1		1			
Right caudate				1	1	
Left caudate		2		1		2

Note: DS, deficit schizophrenia; NDS, nondeficit schizophrenia; HCS, healthy comparison subjects.

(1) negative symptoms (sum of global scores on the alogia, anhedonia, affective flattening, and avolition subscales of the SANS); (2) reality distortion (sum of global scores on the hallucinations and delusions subscales of the SAPS); and (3) disorganization (sum of global scores on the formal thought disorder and bizarre behavior subscales of the SAPS). For the EBPRS, only the total score was included in the analyses. Two-way ANOVAs for repeated measures were used on SANS/SAPS dimensions and Strauss-Carpenter Outcome Scale (SCOS) subscales (group, between; dimensions/subscales, within); independent one-way ANOVAs were performed on the EBPRS total score to test group differences between patients with DS and those with NDS.

Multivariate Analysis of Covariance (MANCOVA) was performed to compare MRI data obtained in the 3 groups of subjects. Diagnosis and gender were grouping factors, the brain structures of interest (lateral ventricles, DLPFCs, cingulate gyri, temporal lobes, hippocampi, caudate nuclei, putamen, and globus pallidi) and hemisphere (right, left) were within factors, and age was the covariate. Univariate follow-up tests were carried out only when a significant main effect or interaction had been found in the multivariate test.

To check whether eventual differences between patient groups were influenced by the site of MRI recording, a further MANCOVA was carried out, in which the site was added as a covariate.

All analyses were considered significant when differences were associated to a P value $< .05$. The software STATISTICA ver. 6 (StatSoft Italia srl., 2003; www.statsoft.it) was used in all the steps of statistical analysis.

Results

Clinical Findings

There were no significant differences between DS and NDS patients in terms of age at illness onset, duration of illness, and EBPRS score (table 2). ANOVA on the 3 psychopathological dimensions revealed a significant interaction dimension × syndrome ($F = 7.13$, $df = 2, 126$, $P < .002$). Patients with DS, as compared with those with NDS, had higher scores on the negative dimension (Tukey's HSD, $P < .01$). On the SCOS, a significant interaction SCOS subscale × syndrome was found ($F = 3.83$, $df = 3, 186$, $P < .01$), due to lower scores (indicating worse outcome) on the subscale "social relationships" in DS than in NDS patients (Tukey's HSD, $P < .008$). Three patients in the deficit group were not receiving antipsychotic drugs. Among patients treated with antipsychotics, the mean current antipsychotic dose, expressed in chlorpromazine equivalents, was higher in patients with NDS than in those with DS, but the difference did not reach the level of statistical significance ($F = 3.68$, $df = 1, 62$, $P = .06$). There was no difference between the deficit and nondeficit patient groups as to

Table 2. Subjects' Demographic Data and Clinical Characteristics of the 2 Patients' Subgroups

	Patients With DS	Patients With NDS	HCS
Number (male/female)	34 (25/9)	32 (26/6)	31 (21/10)
Age (y)	35.8 ± 7.4	34.2 ± 8.1	34.4 ± 8.3
Education (y)	11.4 ± 3.0	11.4 ± 3.6	12.4 ± 2.4
Age at illness onset (y)	22.4 ± 3.7	21.3 ± 4.1	—
Duration of illness (y)	14.0 ± 8.0	14.1 ± 6.6	—
EBPRS	44.3 ± 6.9	45.0 ± 9.9	—
Reality distortion	3.1 ± 2.7	4.3 ± 3.0	—
Negative dimension	12.5 ± 3.2*	10.4 ± 3.3	—
Disorganization	2.4 ± 1.9	2.9 ± 1.9	
SCOS social relationships	1.1 ± 1.4*	2.1 ± 1.5	—
Antipsychotic drug dose	428.9 ± 282.2	563.2 ± 277.8	—

Note: DS, deficit schizophrenia; NDS, nondeficit schizophrenia; HCS, healthy comparison subjects; EBPRS, Extended Brief Psychiatric Rating Scale; SCOS, Strauss-Carpenter Outcome Scale. *$P < .01$.

the type of antipsychotic treatment they were receiving (second-generation antipsychotics only: 71% and 59.4%, respectively; first-generation antipsychotics only: 19.3% and 25%, respectively; combination: 9.7% and 15.6%, respectively).

MRI Findings

MANCOVA on the evaluated brain structures (lateral ventricles, DLPFCs, cingulate gyri, temporal lobes, hippocampi, caudate nuclei, putamen, and globus pallidi) showed a significant effect of diagnosis (Hotelling $T^2 = 1.3$; F = 3.01; $df = 32, 148$; $P < .000004$), a significant interaction diagnosis × structure (Hotelling $T^2 = 0.59$; F = 3.34; $df = 14, 168$; $P < .0001$) and diagnosis × structure × hemisphere (Hotelling $T^2 = 0.35$; F = 2.05; $df = 14, 166$; $P < .02$). No significant main effect of gender or interactions involving gender was found. These significant results were further investigated by Tukey's HSD procedure, which provided the results described below and in table 3.

Lateral Ventricles. No significant difference was observed between DS and NDS patients. Lateral ventricles were significantly larger in patients with NDS than in healthy comparison subjects ($P < .00005$; $P < .01$, for the right and left ventricles, respectively). No significant difference was detected when comparing DS patients with healthy subjects.

Dorsolateral Prefrontal Cortices. No significant difference was observed between DS and NDS patients for this structure. The right and the left DLPFCs were significantly smaller in both patient groups than in healthy subjects (for NDS: $P < .00005$, for both right and left DLPFCs; for DS: $P < .003$ and $P < .00005$, respectively).

Temporal Lobes. The right temporal lobe volume was significantly smaller in patients with DS when compared with those with NDS ($P < .00005$). When the 2 clinical variables showing a significant difference between the 2 patient groups were used as covariate in the analysis, no group difference was found. The right and the left temporal lobes were significantly smaller in both patient groups than in healthy subjects ($P < .00005$ for all comparisons).

Cingulate Gyri. No difference between the 2 patient groups was observed for this structure. In patients with NDS, the left cingulate gyrus was smaller than in healthy controls ($P < .0003$). No difference between patients with DS and healthy subjects was found.

Other Structures. No group difference was observed for hippocampi, caudate nuclei, globus pallidi, and putamen.

Statistical Analyses Carried Out Retaining the Outlier Values. As shown in table 3, statistical analyses carried out without replacing the outlier values with group means produced only marginal changes as compared with results described above. These changes involved the significance levels but not the pattern of group differences.

Statistical Analysis Carried Out to Control for the Effect of Site. The MANCOVA carried out to control for the possible influence of the site of MRI acquisition on group differences did not show significant interactions site × diagnosis (Hotelling $T^2 = 1.92$; F = 1. 31; $df = 48, 98$; $P < .13$), site × diagnosis × brain structure (Hotelling $T^2 = 0.54$; F = 1.07; $df = 21, 125$; $P < .38$), and site × diagnosis × hemisphere × brain structure (Hotelling $T^2 = 0.77$; F = 1.52; $df = 21, 125$; $P < .1$).

Discussion

The present study provides the largest set of MRI findings in patients with DS published so far. According to our results, lateral ventricles were enlarged only in NDS patients as compared with healthy subjects. The failure to find enlarged lateral ventricles in patients with DS is in line with the observation of Buchanan et al[30] of more pronounced structural abnormalities in NDS than in DS patients. Although the finding might appear counterintuitive, based on the assumption that enlarged ventricles are associated with negative symptoms and poor outcome, it should be pointed out that correlates of ventricular enlargement have been variable[47,48] and included higher

Table 3. Brain Regional Volumes, Expressed as Percentages of Total Intracranial Volume, in Patients and Healthy Comparison Subjects

	Patients With DS	Patients With NDS	HCS
Structure	Regional volumes (mean ± SD)		
Right lateral ventricle	0.5220 ± 0.2298	0.6163 ± 0.2676*** [c]	0.4296 ± 0.1556
Left lateral ventricle	0.5646 ± 0.2930	0.6511 ± 0.2820* [b]	0.5168 ± 0.2112
Right dorsolateral prefrontal cortex	1.3648 ± 0.3541** [c]	1.2529 ± 0.3667*** [c]	1.5092 ± 0.2194
Left dorsolateral prefrontal cortex	1.1355 ± 0.3547*** [c]	1.1008 ± 0.3164*** [c]	1.3869 ± 0.1483
Right hippocampus	1.5760 ± 0.2931	1.6430 ± 0.2658	1.6751 ± 0.2156
Left hippocampus	1.5869 ± 0.3107	1.6870 ± 0.2596	1.6850 ± 0.1992
Right cingulate cortex	1.3105 ± 0.1184	1.2233 ± 0.1461	1.3306 ± 0.1555
Left cingulate cortex	1.2349 ± 0.2143	1.1528 ± 0.1182** [a]	1.3130 ± 0.1698
Right temporal lobe	6.2249 ± 0.6157[#] *** [c,d]	6.4170 ± 0.5789*** [c]	6.6942 ± 0.6175
Left temporal lobe	6.5539 ± 0.5328*** [c]	6.5250 ± 0.5224*** [c]	6.8904 ± 0.5373
Right putamen	0.2241 ± 0.0419	0.2428 ± 0.0425	0.2104 ± 0.0418
Left putamen	0.2253 ± 0.0473	0.2415 ± 0.0484	0.2107 ± 0.0411
Right pallidum	0.0877 ± 0.0234	0.0835 ± 0.0256	0.0705 ± 0.0220
Left pallidum	0.0807 ± 0.0215	0.0875 ± 0.0295	0.0743 ± 0.0211
Right caudate	0.2255 ± 0.0381	0.2453 ± 0.0469	0.2272 ± 0.0295
Left caudate	0.2102 ± 0.0392	0.2220 ± 0.0347	0.2167 ± 0.0243

Note: DS, deficit schizophrenia; NDS, nondeficit schizophrenia; HCS, healthy comparison subjects. Significant difference with respect to healthy controls, $^{*}P < .02$; $^{**}P < .005$; $^{***}P < .000005$. Significant difference between patients with deficit schizophrenia and those with nondeficit schizophrenia, $^{\#}P < .0000005$. Significant difference with respect to healthy controls, without replacing outlier values with group mean values, $^{a}P < .01$; $^{b}P < .0001$; $^{c}P < .00005$. Significant difference between patients with deficit schizophrenia and those with nondeficit schizophrenia, without replacing outlier values with group mean values, $^{d}P < .02$.

IQ and better premorbid abilities.[49,50] It is worth mentioning that higher IQ and better premorbid functioning during childhood and early adolescence have been reported in patients with NDS with respect to those with DS.[2,5,6] According to DeQuardo et al,[51] 2 developmental processes may operate in schizophrenia: one with adolescent onset associated with relatively normal childhood social function and IQ and with increased ventricular size and another one with an onset early in life associated with poor premorbid function during childhood, lower IQ, and normal ventricles. More abnormal scans in patients with NDS might reflect progressive ventricular enlargement, possibly related to the excitotoxic effect of repeated psychotic episodes, and be associated with normal early premorbid adjustment and general cognitive abilities, while less abnormal scans in patients with DS might reflect an early onset nonprogressive developmental process, interfering since childhood, with the acquisition of basic cognitive and social skills. The reverse finding of more abnormal right temporal lobe in DS patients might appear in contrast with this interpretation; however, an early neurodevelopmental process interfering with the development of this structure only in patients with DS might explain both the structural finding reported above and the poor premorbid adjustment and social cognition observed in this subgroup.[5–7] The possibility that brain nonprogressive changes occurring in psychotic patients arise at different sites to areas affected by progressive abnormalities was suggested by a recent MRI study in people at ultrahigh risk for the development of psychosis.[52]

For the cingulate gyri, our data showed significantly smaller volumes in NDS, but not in DS, as compared with healthy controls. The failure to find differences in the DS group cannot be attributed to differences in sample size because this group is even larger than the NDS one. It is worth noting that studies investigating either the anterior or the posterior cingulate in subjects with schizophrenia have actually reported conflicting results (see Honea et al[53] for a review). According to our findings, the heterogeneity of studied populations may explain the negative findings reported by several studies.

The reduced volume of the DLPFC in our patients is in line with previously reported findings in subjects with schizophrenia.[54–57] The lack of significant differences between the 2 patient subgroups in DLPFC volume is in line with the findings of Buchanan et al.[30] However, at odds with those findings, we found that both patient groups had smaller DLPFC than healthy controls. Methodological differences may account for the discrepancy, as in the study of Buchanan et al[30] the difference included both the orbitofrontal and the DLPFC, while our measures were

limited to the DLPFC. Future studies including measures of the orbitofrontal cortex might contribute to clarify the reasons underlying this discrepancy.

Both patient groups had smaller temporal lobes than healthy subjects, but those with DS had significantly reduced right temporal lobe volume as compared with NDS ones. It might be tempting to conclude that the more severe abnormality of this brain structure in patients with DS contributes to their greater impairment in social functioning, in particular in social relationships, given the role of the right temporal lobe in important aspects of social communication, such as language prosody and face recognition.[58–60] The lack of significant group differences following the inclusion of the negative dimension and interpersonal relationships as covariates in the analysis does not rule out this interpretation as the 3 concepts (DS, negative dimension, and interpersonal relationships) do have a great degree of overlap.

The volumes of caudate, globus pallidus, putamen, and hippocampus did not differ among groups.

As to the basal ganglia, most of the studies reporting positive findings found an increase in the volume of these structures in patients with schizophrenia as compared with healthy controls, probably due to treatment with neuroleptics.[61] When considering both DS and NDS patients included in our study, 65% were treated with second-generation antipsychotics only, and this might account for the negative finding.

Although the majority of MRI studies found smaller hippocampi either unilaterally or bilaterally in patients with schizophrenia than in healthy controls, negative findings were also reported.[61–64] Differences in slice thickness, separation/nonseparation of anterior from posterior hippocampal formation, and the inclusion/noninclusion of the amygdala in the measurement of the hippocampal complex might explain discrepancies in the findings.

Several limitations of the present study should be acknowledged. MRI data were collected using different scanners; it is unlikely, however, that this procedure influenced the pattern of findings. In designing the MRI acquisition protocol, best solutions to minimize differences in parameter settings and to ensure the highest comparability among sites were discussed and adopted (choice of comparable acquisition parameters to minimize inhomogeneity among sites, beforehand analysis at the central reference site of sample images to ensure correct execution of the specified imaging sequences and to verify compatibility between data format). Additionally, calculated relaxation rate maps are relatively stable, as compared with image signal intensities, thus providing a robust base for segmentation, as far as differences in scanners and imaging parameters are concerned.[39,65] A further limitation might be represented by the loss of part of the recruited sample due to subjects' refusal to participate in MRI procedures, lack of cooperation during MRI acquisition, or technical reasons. However, clinical and demographic characteristics of the included subjects did not differ from those of the whole group. The use of a prevalence sample (including chronic patients with a long-term exposure to drug treatment) might also limit the generalizability of the findings. Future studies in first-episode drug-naive cases are needed to confirm our results.

In conclusion, in comparison with healthy controls, lateral ventricles were enlarged and cingulate gyri were smaller only in patients with NDS; the DLPFC and the temporal lobe showed less volume in both groups. The only significant difference between the 2 patient groups involved the right temporal lobe, which was smaller in DS than in NDS patients. These findings do not support the hypothesis that DS represent the extreme end of a severity continuum within schizophrenia: in this case, a more severe degree of the same abnormalities would be expected in DS than in NDS patients; in our data, most of the abnormalities were seen in NDS but not in DS patients. The only exception was the smaller volume of the right temporal lobe in DS than in NDS, which probably accounts for some characteristics of this patient subgroup, such as greater impairment in social communication.

Future studies are needed to complement the present findings by investigating, in both patient groups and in healthy subjects, subcortical regions involved in social cognition, different segments of the lateral ventricles, and different subregions within the cingulate gyri, the hippocampi, and the temporal lobes.

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