

Gray Matter Changes in Patients with Deficit Schizophrenia and Non-Deficit Schizophrenia



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Objectives: Reduced gray matter volume is a frequently reported finding in brain imaging studies performed with schizophrenia patients. Some studies suggest a probable link between the negative symptoms of schizophrenia and gray matter loss; however, some of the negative symptoms observed in schizophrenia patients are not primarily linked to the core of schizophrenia. This study aimed to compare gray matter volumes in patients with primary negative symptoms (deficit schizophrenia [DS]), non-DS (NDS) patients, and healthy controls.

Materials and Methods: The study included 11 DS patients, 18 non-DS patients, and 17 healthy controls. Magnetic resonance imaging (MRI) was performed using a 1.5 Tesla MR unit. The Schedule for Deficit Syndrome (SDS) was used to determine which patients were DS and non-DS. MR images were compared using voxel-based morphometry (VBM) analysis.

Results: Contrary to expectations, no evidence to support less gray matter in DS patients than in NDS patients was observed. Furthermore, NDS patients had less gray matter volume in several brain regions (frontal and temporal cortices) than did the DS patients. All patients had perisylvian gray matter volume deficits, though the NDS patients had more widespread volume deficiencies.

Conclusion: No evidence to support the hypothesis that DS patients have less gray matter volume than those of NDS patients was observed. On the contrary, DS patients had more gray matter volume in some regions; the differences observed in gray matter volume in these brain regions between the 2 patient groups may be responsible for the differences in their clinical manifestations.

Keywords: Schizophrenia, deficit syndrome, magnetic resonance imaging, frontal lobe, gray matter, temporal lobes, dorsolateral prefrontal cortex, cingulate gyri

INTRODUCTION

One of the main obstacles in schizophrenia research is the heterogeneity of the clinical appearance of schizophrenia patients. Since Kraepelin and Bleuler, this heterogeneity problem has resulted in researchers grouping the symptoms of schizophrenia in different clusters (Galderisi and Maj 2009; Crow 1985). Several research groups suggested that the negative symptoms were the core of schizophrenia and the positive symptoms might be transient in many of the patients (Andreasen 1982; Crow 1980). The negative symptoms that Crow identified and suggested for type-2 schizophrenia are

affective bluntness and poverty of speech, which are thought to be resistant to treatment (Crow 1985). Nevertheless, Carpenter et al. (1988) tried to identify a more homogenous subtype of schizophrenia, and pointed out that the negative symptoms can fluctuate during the course of the illness, depending on their causes (e.g. medication side effects, contribution of psychotic symptoms, and environmental deprivation).

Deficit schizophrenia (DS), as described by Carpenter et al. (1988), is thought to be a valid and reliable diagnosis (Galderisi and Maj 2009). DS is diagnosed in patients with persistent negative symptoms that may occur during recovery

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from psychotic exacerbation and are not fully accounted for depression or anxiety, drug effects, or environmental deprivation. The negative symptoms associated with DS are restricted affect, diminished emotional range, poverty of speech with curbing interest and decrease in curiosity, diminished sense of purpose and diminished social drive. Studies have confirmed that DS is a stable diagnosis (please see Galderisi and Maj [2009] for an extensive review).

Assessment of DS as a subtype of schizophrenia led to the hypothesis that such patients may differ from other schizophrenia patients regarding brain structure and function (Carpenter et al. 1988). Indeed, Gonul et al. (2003) reported that DS patients had lower cerebral blood flow in the frontal lobes than other schizophrenia patients. The first study that compared brain volume in DS and non-DS (NDS) patients was conducted by Buchanan et al. (1993), who reported that DS patients had greater frontal lobe volume than NDS patients. Although subsequent studies (Galderisi et al. 2008; Quarantelli et al. 2002) confirmed this finding, a recent study by Cascella et al. (2010) reported smaller frontal and temporal lobe volume in DS patients than in NDS patients. Moreover, some studies did not observe any regional brain volumetric differences between DS and NDS patients (Galderisi and Maj 2009). The present study aimed to measure and compare gray matter volume in DS patients, NDS patients, and healthy controls using MRI and voxel-based morphometry (VBM), and to determine in which brain regions there were volumetric differences.

MATERIALS AND METHODS

Participants

The study included 44 patients diagnosed as schizophrenia according to DSM-IV TR. The patients were treated at Ege University School of Medicine, Department of Psychiatry and its associated clinics. None of the patients were experiencing psychotic exacerbation, defined as having positive symptoms that could lead to hospitalization to prevent self harm, harm to another person. None of the patients had been hospitalized during the 6 months prior to recruitment. The patients and healthy controls were administered the Structured Clinical Interview for DSM-IV (SCID-I) (First et al. 1997). The diagnostic reliability of SCID-I is high, as it aims to diagnose a patient by following instructions and it requires the questions to be asked as it is written in the manual. Additional information from the family and friends were used to increase the reliability of the diagnoses (Corapcioglu et al. 1999; First et al. 1997).

In the patient group the diagnosis of DS was confirmed based on the Turkish version of the Schedule for Deficit Syndrome (SDS) (Citak et al. 2006; Kirkpatrick et al. 1993, 1989). SDS

is a semi-structured assessment tool used to differentiate patients with and without deficit syndrome. First, the severity of 6 negative symptoms (restricted affect, diminished emotional range, poverty of speech, curbing of interests, diminished sense of purpose, and diminished social drive) is scored on a scale of 0–4 (0 = normal and 4 = severe). Next, the duration of the 6 symptoms is determined (a minimum duration of 12 months is required). Lastly, it is determined if the symptoms are due to primary factors (that they are not a consequence of the secondary to factors other than the disease process). All of the patients were assessed by 2 experienced researchers trained in the use of SDS. Only the patients for whom a consensus for the diagnosis of DS or non-DS was reached by two researchers (B.Z. and A.S.G) were included in the study.

On the day MRI was performed, the patients were administered the Positive and Negative Symptoms Scale (PANNS), and their antipsychotic medication doses were recorded based on chlorpromazine equivalent doses (Woods 2003). PANNS includes 3 subscales, including 7 items for each of the positive and negative symptom clusters and 16 items for the general psychopathology subscale that evaluates the presence and severity of the symptoms. Data regarding the patient can be obtained both from the patient and his/her relatives (Kostakoglu et al. 1999; Kay et al. 1987).

In all, 12 patients were excluded from the study due to inadequate follow-up duration and ambiguous symptoms (it was not possible to classify the symptoms), 2 patients withdrew their informed consent, and 1 patient was excluded from the study due to a tumor in the cingulate cortex. MRI was performed in the remaining 29 patients, and these images were used for analysis.

The control group consisted of 17 healthy individuals without an axis-I disorder, according to assessment by SCID-I. None of the controls had a first-degree relative diagnosed as schizophrenia or bipolar disorder. Other exclusion criteria were as follows: having a past or present neurological or other medical illness, a history of head trauma with loss of consciousness for ≥ 3 min, substance abuse or dependence other than nicotine, and left handedness based on the Edinburgh Handedness Inventory (Oldfield 1971).

The study protocol was approved by the Ege University Ethics Committee and was supported by the Ege University Commission of Scientific Research (project grant number: 05-Tip-028). Informed consent was provided by all the participants, and a researcher other than the one that obtained informed consent evaluated whether or not the participants understood the content of the consent.

Magnetic Resonance Imaging

MRI was performed using a 1.5 Tesla MR unit (Magnetom Vision Siemens, Erlangen, Germany) at Ege University,

TABLE 1. Comparison of demographic and clinical variables between the study groups

	DS (n = 11)	NDS (n = 18)	Control (n = 17)	Comparison
Age (years)	32.36 ± 8.23	40.77 ± 12.27	33.82 ± 10.11	F = 2.8, df = 2,45, P > 0.05
Sex (male/female)	7/4	9/9	9/8	X ² = 1.57, df = 2, P > 0.05
Education (years)	7.88 ± 4.88	9.23 ± 3.81	15.56 ± 3.6	F = 14.7, df = 2,45, P < 0.001
Duration of illness (months)	81 ± 33.8	146.88 ± 95.41	-----	T = 1.88, df = 24, P > 0.05
Age of onset (years)	24.25 ± 8.31	29.23 ± 13.37	-----	T = 0.9, df = 24, P > 0.05
PANSS				
Positive	13.1 ± 5.36	13.4 ± 6.52		T = 0.11, df = 26, P > 0.05
Negative	31.4 ± 9.1	16.2 ± 7.35		T = 4.8, df = 26, P < 0.001
General Psychopathology	41.2 ± 6.4	34 ± 9.58		T = 2.11, df = 26, P = 0.04
Total	89.5 ± 15.2	60.94 ± 15.3	----	T = 4.33, df = 26, P < 0.05
Antipsychotic medication dose (mg)*	543.57 ± 613.7	390.81 ± 277.1	----	T = 0.8, df = 24, P > 0.05
Total grey matter (cm ³)	668.834	652.069a	718.925a'	F = 3.91, df = 2,44, P = 0.027
Total white matter (cm ³)	486.434	492.770	497.632	F = 0.15, df = 2,44, P > 0.05
Total cerebrospinal fluid (cm ³)	578.315	571.021	513.538	F = 1.5, df = 2,44, P > 0.05
Total brain volume (cm ³)	1733.584	1715.860	1729.746	F = 0.5, df = 2,44, P > 0.05

*Chlorpromazine equivalent doses.

a-a': Post-hoc Bonferroni comparison, P = 0.029.

PANSS: Positive and Negative Symptoms Scale.

School of Medicine, Department of Radiodiagnostics. In addition to routine evaluation sequences, T-1 weighted 3D-FLASH sequences were obtained (TR: 2300 ms; TE: 3.93 ms; slice thickness: 1 mm; flip angle: 12°; dimension: 3D; FOV read: 256 mm; FOV phase: 100 %; bandwidth: 130 Hz/Px; echo spacing: 9.9 ms).

Post-processing of MR images

All MR images were transformed from the DICOM (Digital Imaging and Communications in Medicine) format to the NIFTI (Neuroimaging Informatics Technology Initiative) format using Statistical Parametric Mapping (SPM) v.8.0 (<http://www.fil.ion.ucl.ac.uk/spm/>) after the images were given code names independent of the participants' names. Then, all images were evaluated by a radiologist (O.K.) to detect any errors stemming from MRI or anatomical abnormalities. Coordinates (x, y, and z) were reset at the anterior commissure in all images. Images were segmented using SPM v.8.0 to grey matter, white matter, and cerebrospinal fluid. New templates were subsequently produced using the SPM v.8.0 DARTEL (diffeomorphic anatomical registration through exponentiated lie algebra) function. The GM template was normalized to MNI space and the resulting deformations were applied to the images of each participant. Finally all of the images were smoothed with 8 mm of kernel.

Statistics

The Chi-squared test was used for categorical variables, Student's t-test was used for continuous variables, and univariate analysis of variance (ANOVA) was employed for 3-way

comparisons; P values <0.05 were accepted as statistically significant. General linear modeling was used for statistical parametric modeling; age, sex and total brain volume were included as confounding factors in the analysis matrix. First, analysis of the comparison of the 3 groups in the general linear model was performed via ANOVA, and the consequent subgroups were compared using the post-hoc t-test. To preclude any false negative findings a P value <0.001 and clusters >200 voxels were accepted as significant for voxel based morphometry (VBM).

RESULTS

Comparison of the demographic and clinical variables

There weren't any significant differences in age or gender between the groups (Table 1). As expected, the duration of education was shorter in the schizophrenia patients than in the control group. Although not significantly different, the age of onset was earlier and illness duration was shorter in the DS patients (Table 1). Positive symptom scores in the DS patients (n = 11) and NDS patients (n = 18) were similar, although the DS patients had higher negative and general psychopathology scores (Table 1). Antipsychotic medication doses were similar among schizophrenia groups when converted to chlorpromazine equivalent doses (Woods 2003).

Comparison of grey matter

The DS and NDS patients had less grey matter volume than the controls (Table 1), whereas total gray matter volume did not differ significantly between the DS and NDS patients (F

TABLE 2. ANOVA of the 3 groups. All of the results have a P value <0.001 and volume differences <200 mm³ were discarded (coordinates are given according to the Talairach Atlas).

Brodman's area	Region	Apex x/y/z coordinates	Cluster size (mm ³)	F value
Left 9	Left DLPFC	-24/35/33	1000	22.39
Right 22	Right STG	56/3/0	1503	19.97
Left 22	Left STG	-56/3/-2	4131	17.47
Right 10	Right ant PFC	21/51/19	2899	17.45
Left 9	Left DLPFC	-41/12/34	819	15.91
N/A	Culmen	-45/-48/-23	374	15.70
Right 8	Right FEF	32/26/51	328	14.78
Right 38	Right temporopolar cortex	50/12/-29	945	13.76
Left 21	Left MTG	-54/6/-32	923	12.85
Right 47	Right inferior PFC	54/38/-6	362	12.17
Left 31	Left posterior cingulate	-8/-27/34	1077	12.15
Left 10	Left anterior PFC	-26/59/0	832	11.92
Left 30	Left parahippocampal gyrus	-12/-34/-3	334	11.79
Left 39	Left angular gyrus	-50/-73/21	244	11.50

DLPFC: Dorsolateral prefrontal cortex; FEF: frontal eye fields; MTG: medial temporal gyrus; N/A: not applicable; PFC: prefrontal cortex; STG: superior temporal gyrus.

= 0.5 df = 2,44 P > 0.05). ANOVA showed that there was a significant disease effect on grey matter volume in the prefrontal cortex, temporal cortex, posterior cingulate cortex, and cerebellum, based on comparison of the 3 groups via VBM (Table 2).

Comparison of the control group and the DS group

The post-hoc t-test showed that the DS patients had less grey matter volume in the prefrontal cortex, temporal cortex, and cerebellum than the controls (Table 3, Figure 1).

Comparison of the control group and the NDS group

Widespread volume deficits were observed in the NDS group, as compared to the controls according to the post-hoc t-test (Table 4, Figure 2).

Comparison of the DS and NDS groups

Based on the t-test, grey matter volume was similar in all regions imaged in the DS and NDS groups, except for the left dorsolateral prefrontal cortex (cluster size: 232 mm³, t = 4.53) and left medial temporal gyrus (cluster size: 340 mm³, t = 4.35), which were larger in the DS group (Table 5, Figure 1).

DISCUSSION

The most important finding of the present study is that the grey matter volume in the frontal and temporal regions in the NDS patients was smaller than that in the DS patients, and the volume deficit was more prominent in the dorsolateral prefrontal cortex (BA 9) and medial temporal gyrus (BA 21). Grey matter volume in the frontal and temporal cortical

regions was smaller in the DS patients than in the controls. NDS patients had widespread grey matter volume deficits, as compared to the control group. As compared to the control group, grey matter volume in the perisylvian regions in the DS and NDS groups was smaller.

Comparison of brain structures based on MRI between the schizophrenia patients and controls showed that the most consistent findings of volume deficit were observed in the left superior and the medial temporal regions (Cascella et al. 2010; Honea et al. 2005). In an extensive meta-analysis by Honea et al. (2005), it was reported that using a kernel size between 4 and 8 mm provides ideal statistical evaluation, whereas values above this interval may be inadequate for observing differences and use of lower values may result in false negative results. In the present study, which used a kernel size of 8 mm, significant volume deficits were observed in the superior temporal gyrus and medial temporal gyrus regions in the DS and NDS groups, especially on the left side, as compared to the control group. We think the bulk of schizophrenia symptoms may stem from these brain regions.

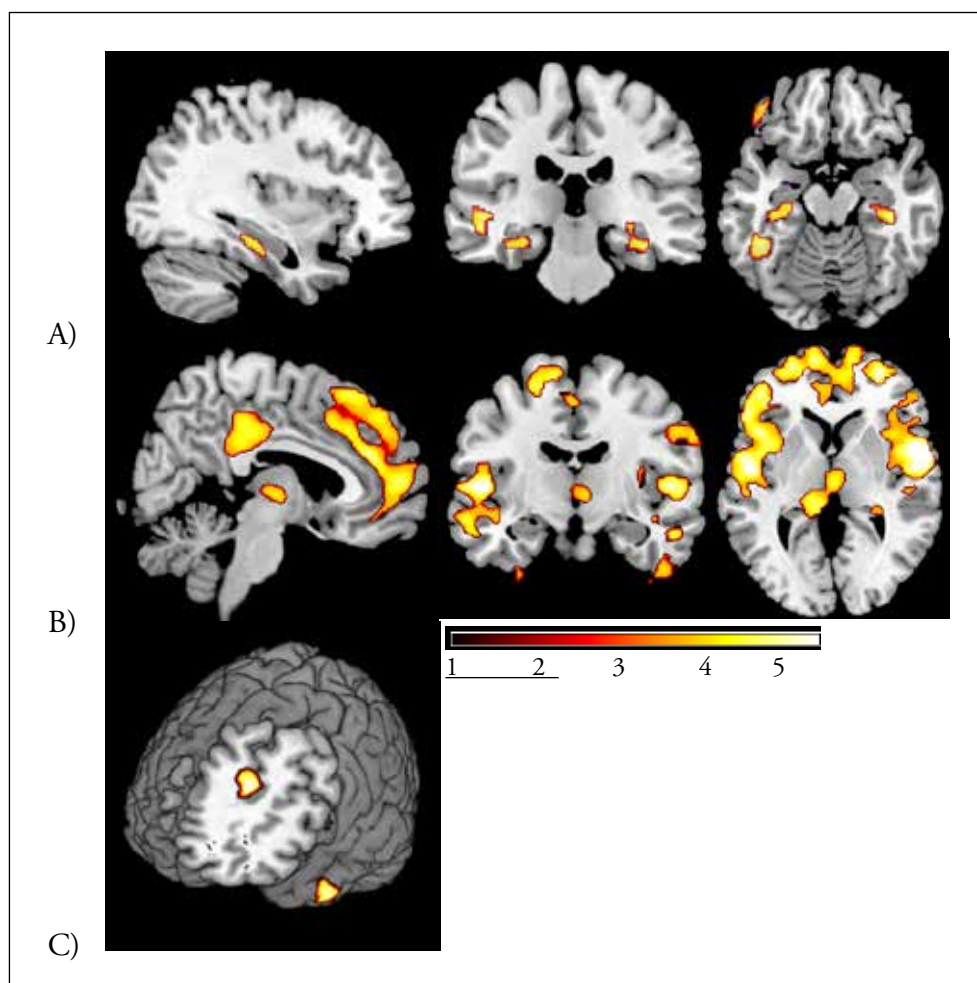
The grey matter volume deficits observed in the perisylvian region in the DS and NDS groups have been known for a long time. In the beginning of the 20th century Southard and Kraepelin almost concurrently proposed that the psychotic symptoms of schizophrenia originated from the suprasylvian and superior temporal regions (Shenton et al. 2001). Perisylvian grey matter is composed of superior temporal gyrus, insula, inferior parietal lobule (supramarginal gyrus) and inferior frontal gyrus (Broca's area) (Koutsouleris et al. 2008). The heteromodal association cortex, including the posterior superior temporal gyrus, inferior parietal lobule, Broca's area, and dorsolateral prefrontal cortex, was suggested

TABLE 3. Grey matter volume differences based on t-test comparison of the control group and the DS group (coordinates are given according to the Talairach Atlas). All of the results have a P value <0.001 and volume differences <200 mm³ were discarded.

Brodmann's area	Region	Apex x/y/z coordinates	Cluster size (mm ³)	t value
N/A	Culmen	-45/-48/-21	560	5.11
Left 21	Left STG	-50/-24/-2	507	4.59
Left 45	Left inferior frontal cortex, triangular region (Broca's area)	-54/26/1	1386	4.42
Right 36	Right parahippocampus	38/-27/-17	261	4.38
Right 47	Right inferior PFC	53/20/-5	681	4.2
Left 36	Left parahippocampus	-38/-28/-15	211	3.8
Left 31	Left posterior cingulate, precuneus	-14/-66/22	350	3.72

N/A: not applicable; PFC: prefrontal cortex; STG: superior temporal gyrus.

FIGURE 1. Images of group comparisons acquired via SPM v.8.0. A. Comparison of the control group and DS group showed grey matter deficits in the temporal cortex (especially the bilateral hippocampi, left superior temporal cortex, and left inferior frontal cortex). B. Comparison of the control group and NDS group showed more diffuse grey matter deficits in the frontal, cingulate, and temporal cortices. C. Three-dimensional view of the comparison between the DS and NDS groups. Greater left dorsolateral prefrontal cortex and left medial temporal gyrus volume was observed in the DS group (Table 5). T-scores are represented by the colored bar.



to be the core region for schizophrenia. This heteromodal association cortex superposes with the perisylvian cortical region. Indeed, the supramarginal and angular gyri that constitute the inferior parietal lobule are an important part of the semantic-lexical network in which words are given meaning and transformed into thoughts (Shenton et al. 2001). The anterior region of the superior temporal gyrus, namely the temporopolar cortex (a limbic region with extensive connections

with other limbic cortical and subcortical structures) works in concert with the posterior superior temporal gyrus, which has an important role in the comprehension of speech per se, and its underlying meaning. The temporopolar cortex acts as the heteromodal association cortex, processing social and emotional information (Olson et al. 2007). The pars triangularis of the inferior frontal cortex, along with the pars opercularis, constitutes Broca's area, which is responsible for

TABLE 4. Grey matter volume differences based on t-test comparison of the control group and NDS group (coordinates are given according to the Talairach Atlas). All of the results have a P value <0.001 and volume differences <200 mm³ were discarded.

Brodmann's area	Region	Apex x/y/z coordinates	Cluster size (mm ³)	t value
Left 9	Left DLPFC	-24/35/31	36550	6.53
Right 8	Right FEF	32/26/51	1067	5.37
Right 38	Right temporal area	50/12/-29	3768	5.23
Left 6	Left premotor area	-14/-7/64	3236	4.93
Left 30	Left parahippocampus	-12/-34/-3	1267	4.85
Left 19	Left occipitotemporal cortex	-51/-73/16	635	4.78
N/A	Culmen	-45/-49/-23	245	4.47
Right 40	Right supramarginal gyrus	62/-24/22	305	4.47
Right 40	Right supramarginal gyrus	60/-54/22	565	4.35
Right 21	Right MTG	68/-33/-5	336	4.26
Left 34	Left uncus, entorhinal cortex	-17/3/-20	623	4.10
----	Right hippocampus	30/-30/-2	297	4.05
Right 38	Right temporopolar cortex	41/18/-18	298	3.88

DLPFC: Dorsolateral prefrontal cortex; FEF: frontal eye fields; MTG: medial temporal gyrus; N/A: not applicable.

the generation of speech. This region mainly receives afferent nerve signals from Wernicke's area in the superior temporal cortex (Clark et al. 2010).

Numerous MRI studies reported that schizophrenia patients have perisylvian cortical volume deficits, as in the present study (Figure 2). Sigmundsson et al. (2001) observed perisylvian grey matter volume deficits in the left superior temporal gyrus extending to the pars opercularis of Broca's area when 27 DS patients were compared to healthy controls. Buchanan et al. (1998) and Davatzikos et al. (2005) also observed that there was less grey matter volume in Broca's area in schizophrenia patients than in healthy controls. Less grey matter volume in the superior temporal gyrus (especially the left side) has been reported in almost every MRI-volumetric study (Moorhead et al. 2004; Spatella et al. 2003; Kubicki et al. 2002; Shapleske et al. 2002; Hulshoff-Pol et al. 2001; Sigmundsson et al. 2001) conducted with schizophrenia patients (there is a recent review by Shenton et al. [2010] on this topic), and was among the most important findings of a meta-analysis by Honea et al. (2005). Many studies have also observed that there is less grey matter volume in the inferior parietal lobule (Davatzikos et al. 2005; Moorhead et al. 2004; Salgado-Pineda et al. 2004; Kubicki et al. 2002; Frederikse et al. 2000; Niznickiewicz et al. 2000; Goldstein et al. 1999; Schlaepfer et al. 1994) and temporopolar cortex (Kasai et al.

2003; Gur et al. 2000) in schizophrenia patients, as compared to healthy controls.

Crow et al. (2007) suggested that language processing effects psychotic symptoms. According to Crow et al., phonological engrams are represented in Broca's area and Wernicke's area, whereas the concepts and meanings that are the counterparts of these engrams are processed in the right hemisphere. Accordingly, the occipital parietal-temporal cortex in the right hemisphere comprehends the conceptual meaning, whereas the prefrontal cortex (especially the dorsolateral prefrontal cortex) seizes the intentional component. Crow et al. posited that defect in communication between the above-mentioned 4 regions is responsible for the development of psychotic symptoms.

Medial temporal structures (e.g. the hippocampus, parahippocampus, uncus, entorhinal cortex, and amygdala) are frequently observed to be smaller in schizophrenia patients (Davatzikos et al. 2005; Moorhead et al. 2004; Marcelis et al. 2003; Salgado-Pineda et al. 2003; Job et al. 2002; Kubicki et al. 2002; Shapleske et al. 2002; Hulshof Pol et al. 2001; Wright et al. 1999). As such, it is not surprising that medial temporal structures in the present study's schizophrenia patients were smaller than those in the controls, given their important role in dysfunctional emotional and (especially memory-associated) cognitive processing in schizophrenia (Sheanton et al. 2001). Likewise, Honea et al. (2005)

TABLE 5. Grey matter volume differences based on t-test comparison of the DS and NDS groups (coordinates are given according to the Talairach Atlas).

Brodmann's area	Region	Apex x/y/z coordinates	Cluster size (mm ³)	t value
Left 9	Left DLPFC	-24/33/33	232	4.53
Left 21	Left MTG	-53/6/-33	340	4.35

DLPFC: Dorsolateral prefrontal cortex; MTG: medial temporal gyrus.

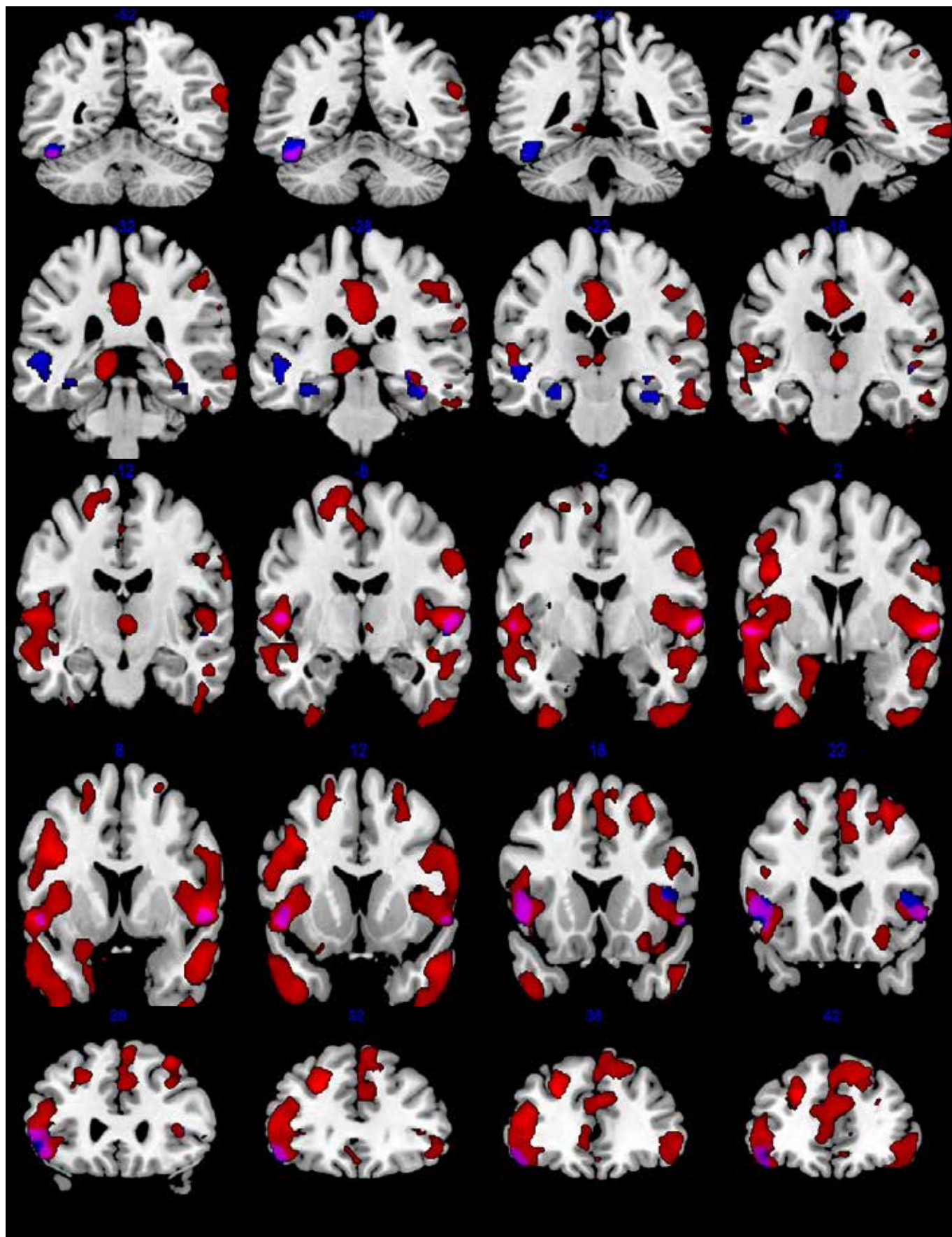


FIGURE 2. Superposed images of the grey matter deficits in the DS and NDS groups when they were compared to healthy controls. Red areas: Healthy controls-NDS patients. Blue areas: Healthy controls-DS patients (numbers represent the Y coordinates).

observed that schizophrenia patients had less hippocampus and parahippocampus volumes.

Interest in the cerebellum in schizophrenia research has increased since Andreasen et al. (1999) proposed the cerebellar dysmetria model based on the dysfunctional cortical-cerebellar-thalamic-cortical loop. Reports of cerebellar volume deficits (Moorhead et al. 2004; Salgado-Pineda et al. 2004; Marcelis et al. 2003) seem to confirm this hypothesis. In the present study cerebellar volume deficit, intensifying in the culmen, was observed in the DS and NDS groups, which supports the cerebellar dysmetria hypothesis, although no further tests were used to verify a direct relationship.

Saccadic eye movements facilitate focusing on a stimulus and are performed by the frontal eye fields. Saccadic eye movement deficits in schizophrenia patients have been reported (Tsuonda et al. 2005). To the best of our knowledge the present study is the first to report frontal eye field volume deficit in NDS patients.

Since Andreasen et al. (1982) reported that the negative symptoms of schizophrenia are associated with larger lateral ventricles; there has been the expectation that DS has more wide-spread neuroanatomical defects, as negative symptoms are more prominent (Carpenter et al. 1988). Yet, only a few structural MRI studies used SDS (Cascella et al. 2010; Galderisi et al. 2008; Quarantelli et al. 2002; Sigmundson et al. 2001; Buchanan et al. 1993); however, these studies have methodological differences and the results regarding grey matter volume deficit are inconsistent. Buchanan et al. (1993) reported that NDS patients have less prefrontal cortex (PFC) volume than DS patients; however, prefrontal cortex volume in DS patients and healthy controls were similar. Buchanan et al. reported that the volumetric difference in the prefrontal cortex originated from white matter and that grey matter volume did not differ between the DS patients ($n = 17$) and NDS patients ($n = 24$). As slice thickness was 3 mm and the segmentation procedure was performed via the software's threshold function, the finding of white matter volume difference should be interpreted with caution due to the limitations of the segmentation procedure and slice thickness. The researchers suggested that the smaller right caudate volume in the DS patients might cause the symptoms of deficit syndrome.

Quarantelli et al. (2002) reported evidence contradicting the common view that DS patients have more widespread neuroanatomical deficits. The study sample of Quarantelli et al. (2002) was enlarged by Galderisi et al. (2008). Surprisingly, Galderisi et al. observed that DS patients and healthy controls had similar lateral ventricle volume, whereas NDS patients had larger lateral ventricles. Likewise, cingulate gyrus volume in the NDS patients was smaller than that in the healthy controls, although cingulate gyrus volume in the DS patients and

healthy controls was similar. Nevertheless, dorsolateral prefrontal cortex volume in both patient samples was less than that in the healthy controls, whereas volumetric differences in the hippocampus, amygdala, and basal ganglia were not observed between groups. The only brain region that was smaller in the DS patients than in the NDS patients was the right temporal cortex. Additionally, temporal cortical volume in both patient groups was smaller than that in the healthy control group. Although this study appears to support the present study's findings, it has some methodological shortcomings. First, MR images were acquired in 4 different MRI units and although this limitation was considered in the statistical evaluation the differences in signal intensity is a potential methodological drawback. Second, use of 4-mm slice thickness precludes assessment of small anatomical regions (e.g. the dorsolateral prefrontal cortex, hippocampus, and basal ganglia). Nonetheless, the study is important regarding its main finding that DS patients do not have more neuroanatomical defects.

Cascella et al. (2010) observed volume deficits in the insula, and frontal and temporal cortices in schizophrenia patients which were more prominent in the left, as compared to healthy controls. Grey matter volume deficits in DS patients were more diffuse, including the bilateral insula, medial temporal gyrus, medial occipital gyrus, superior parietal lobe, and left superior frontal gyrus (BA 6), superior temporal gyrus, thalamus, and precuneus, and right fusiform gyrus, inferior parietal lobe, and cuneus. No brain region in the NDS patients was smaller than in the DS group. The brain regions that best differentiated the patient groups were the bilateral superior frontal gyrus and superior temporal gyrus, and left supplementary motor area (BA 6), anterior cingulate, cuneus, and right putamen. Results reported by Cascella et al. (2010) partially overlap with the present results, in terms of differences between the DS and healthy control groups (i.e. left superior temporal gyrus and precuneus), but contradict the present findings based on comparison of the DS and NDS patients. An interesting finding of the Cascella et al. study is that DS patients had larger overall grey matter volume.

The present study's small sample size is an important limitation. To overcome this limitation we set the level of statistical significance at $P = 0.001$ for evaluating volume differences and discarded volume defects that were $<200 \text{ mm}^3$, which is a large cluster size. The patients and controls were not matched for duration of formal education, which is another limitation, as it is known that years of formal education positively correlate with grey matter volume in the hippocampus (Gonul et al. 2009); however, the level of education in schizophrenia patients was lower than that in healthy controls in numerous studies, and groups were not matched according to this variable (Hulshoff Pol et al. 2004; Davatzikos et al. 2004; Sigmundsson et al. 2001) or no education data were provided

(Salgado-Pineda et al. 2004; Job et al. 2002; Kubicki et al. 2002). Buchanan et al. suggested that the age of onset is earlier in DS patients than in NDS patients. In this aspect, shorter duration of formal education in DS patients can be expected, and has been reported (Buchanan et al. 1993, Cascella et al. 2010).

In conclusion, the present study's findings do not confirm the common view that DS patients have more diffuse grey matter deficits than NDS patients. The present finding that NDS patients had less frontal and temporal cortex volume than the DS patients, suggest that the volumetric difference may be responsible for the disparity in the clinical picture in DS and NDS patients.

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