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A Large Scale (N=400) Investigation of Gray Matter Differences in Schizophrenia Using Optimized Voxel-based Morphometry

Shashwath A. Meda[a,*], **Nicole R. Giuliani**[a], **Vince D. Calhoun**[a,b,c,h], **Kanchana Jagannathan**[a], **David J. Schretlen**[c], **Anne Pulver**[c], **Nicola Cascella**[c], **Matcheri Keshavan**[d], **Wendy Kates**[e], **Robert Buchanan**[f], **Tonmoy Sharma**[g], and **Godfrey D. Pearlson**[a,b,c]

a*Olin Neuropsychiatry Research Center, Institute of Living at Hartford Hospital, 200 Retreat Avenue, Hartford, CT 06106*

b*Dept. of Psychiatry, Yale University School of Medicine, 333 Cedar Street, New Haven, CT 06510*

c*Dept. of Psychiatry, Johns Hopkins University, 600 North Wolfe Street, Baltimore, MD 21287*

d*Dept. of Psychiatry. Wayne State University, University Health Center, Detroit, MI 48202*

e*Dept. of Psychiatry , and Behavioral Science, State University of New York, Upstate Medical University, Syracuse, NY 13210*

f*Maryland Psychiatric Research Center, Department of Psychiatry, University of Maryland, P.O. Box 21247, Catonsville, MD 21228*

g*Clinical Neuroscience Research Centre, 7 Twisleton Court, Priory Hill, Dartford, DA1 2EN, Kent, UK*

h*The MIND research network, University of New Mexico, Albuquerque, NM 87131*

Abstract

Background—Many studies have employed voxel-based morphometry (VBM) of MRI images as an automated method of investigating cortical gray matter differences in schizophrenia. However, results from these studies vary widely, likely due to different methodological or statistical approaches.

Objective—To use VBM to investigate gray matter differences in schizophrenia in a sample significantly larger than any published to date, and to increase statistical power sufficiently to reveal differences missed in smaller analyses.

Methods—Magnetic resonance whole brain images were acquired from four geographic sites, all using the same model 1.5T scanner and software version, and combined to form a sample of 200 patients with both first episode and chronic schizophrenia and 200 healthy controls, matched for age, gender and scanner location. Gray matter concentration was assessed and compared using optimized VBM.

Results—Compared to the healthy controls, schizophrenia patients showed significantly less gray matter concentration in multiple cortical and subcortical regions, some previously unreported.

*Corresponding Author: Shashwath A. Meda, Olin Neuropsychiatry Research Center, Whitehall Building, 200 Retreat Avenue, Hartford, CT 06106, Tel: 860-545-7804, Fax: 860-545-7797, Email: smeda01@harthosp.org.

Overall, we found lower concentrations of gray matter in regions identified in prior studies, most of which reported only subsets of the affected areas.

Conclusions—Gray matter differences in schizophrenia are most comprehensively elucidated using a large, diverse and representative sample.

Keywords

Schizophrenia; Structural MRI; multi-site; voxel based morphometry; gray matter

1. Introduction

MRI studies of schizophrenia report approximately 2% less global gray matter (GM) volume in patients (Wright et al., 2000) and disproportionately less focal GM volume in many (perhaps especially heteromodal association cortex (HASC) regions (Baumann and Bogerts, 1999; Bucahanan et al., 2004; Falkai et al., 2001; Keshavan et al., 2003; Mesulam, 2004; Pearlson et al., 1996; Schlaepfer et al., 1994; Wright et al., 2000).

Lately, investigators have employed voxel-based morphometry (VBM; Ashburner et al., 2000), an efficient whole brain unbiased technique, to examine structural MRI differences. VBM provides automated measures of highly localized regions that may not be investigated in hypothesis-based studies that employ more labor-intensive region of interest (ROI) measures. VBM identifies regional differences in the concentration/volume of gray or white matter between groups, including GM alterations in schizophrenia versus healthy controls (Ananth et al., 2002; Gaser et al., 1999; Hulshoff Pol et al., 2002; Kubicki et al., 2002; Moorhead et al., 2004; Sigmundsson et al., 2001; Sowell et al., 2000; Suzuki et al., 2002; Wilke et al., 2001; Wright et al., 1999). These confirm and extend ROI studies (Gaser et al., 1999; Honea et al., 2005; Job et al., 2002) by increasing the anatomical range of volumetric comparisons. Schizophrenia samples exhibit lower GM concentrations in cingulate gyrus (Hulshoff Pol et al., 2002; Kubicki et al., 2002; Sigmundsson et al., 2001; Sowell et al., 2000), all frontal gyri (Gaser et al., 1999; Moorhead et al., 2004; Suzuki et al., 2002; Wilke et al., 2001), superior temporal gyrus (Gaser et al., 1999; Hulshoff Pol et al., 2002; Kubicki et al., 2002; Sigmundsson et al., 2001; Sowell et al., 2000; Suzuki et al., 2002; Wilke et al., 2001), medial temporal lobe (Hulshoff Pol et al., 2002; Sigmundsson et al., 2001; Suzuki et al., 2002; Wilke et al., 2001), insula (Hulshoff Pol et al., 2002; Kubicki et al., 2002; Sigmundsson et al., 2001;Wright et al., 1999) and thalamus (Ananth et al., 2002; Gaser et al., 1999; Hulshoff Pol et al., 2002; Sowell et al., 2000). Some VBM studies also demonstrate greater concentrations of GM among schizophrenia samples in the basal ganglia (Gaser et al., 1999; Kubicki et al., 2002; Wilke et al., 2001) and cerebellum (Kubicki et al., 2002; Suzuki et al., 2002), with the former perhaps attributable to first-generation antipsychotic treatment.

The statistical power of previous studies, however, has been relatively low, with most samples including fewer than 50 participants (Ananth et al., 2002; Kubicki et al., 2002; Wilke et al., 2001; Wright et al., 1999). These samples are large enough to reveal consistent fronto-temporal differences (Wright et al., 1999; Shenton et al., 2001), but differences in more anatomically variable regions, e.g. inferior parietal lobule, are reported less consistently. According to a recent meta-analysis of VBM studies (Mechelli et al., 2005), differences in the latter areas, though real, are inconsistently found due to the variations in size of smoothing kernels used across studies, the heterogeneity of schizophrenia itself, and failure of small samples to adequately represent the disease. Even though our study was not designed as a prospective multi-center study, similarities in acquisition parameters across the four different sites allowed us to pool data across scanners. By using VBM to investigate GM in a large and diverse schizophrenia sample, we hoped to increase statistical power sufficiently to reveal subtle

differences missed in smaller analyses. Also, by using a sample incorporating patients from varied backgrounds and areas, we aimed to increase generalizabilty of our results.

2. Methods and Materials

2.1. Subjects

We combined data from four separate studies conducted at Johns Hopkins University (JHU), the Maryland Psychiatric Research Center (MPRC), the Institute of Psychiatry, London, UK (IOP), and the Western Psychiatric Institute and Clinic at the University of Pittsburgh (WPIC). Samples were matched for age and gender within each site. The combined sample comprised 200 schizophrenia patients (78 females, mean age = 39.7, SD = 12.0, range 17–81) and 200 matched healthy controls (99 females, mean age = 40.0, SD = 14.8, range 16–79) and contained both first episode and chronic patients (see Table 1).

At each site, schizophrenia or schizoaffective disorder patients were diagnosed using the Structured Clinical Interview for DSM-III-R/DSM-IV (SCID; First et al., 1997; Spitzer et al., 1989), direct assessment, family informants, and past medical records. Healthy controls from the IOP, MPRC and WPIC samples were recruited from a pool of community volunteers; JHU controls were recruited using random-digit dialing as part of a community study (Schretlen et al., 2003). All control subjects were evaluated with the same structured interview as patients and excluded for a history of DSM-III-R/DSM-IV Axis I or Axis II disorder or major mental illness in first-degree relatives. Exclusion criteria for all samples included a history of overt brain disease, mental retardation, head injury with loss of consciousness over 60 minutes, or a diagnosis of substance abuse or dependence within the last 12 months.

2.2. MR imaging parameters

At all sites, whole brain MRIs were obtained on a 1.5T Signa GE scanner (GE Medical Systems, Milwaukee) in the coronal plane using a SPGR three-dimensional imaging sequence with the same software version. Between sites, almost every parameter was identical (35msec TR, 5msec TE, 45° flip angle, 1 excitation, 1.5mm slice thickness, 24cm field of view, and a matrix size of 256 × 256), except for IOP data, which were obtained using a 35° flip angle and a 20cm field of view.

2.3. Data Analysis

All images were visually inspected for orientation and movement artifacts, organized for preprocessing and analyzed using the SPM2 (http://www.fil.ion.ucl.ac.uk/spm/software/spm2/) software running in MATLAB 6.5.1 (The MathWorks, MA, USA).

2.3.1. Template Creation—Template creation utilized images from all 200 control subjects only. The control structural MRI scans were transformed to the same stereotactic space by registering each of the images to the ICBM 152 template (Montreal Neurological Institute). Normalized images were interpolated to voxel dimensions of $1.5mm^3$and segmented into GM, white matter (WM) and cerebrospinal fluid (CSF). Images were then smoothed with an 8mm full-width half-maximum Gaussian kernel and averaged across subjects to create T1, gray, white and CSF templates. The templates were created using only healthy subjects to avoid confounding normalization with possible disease-related patients' data.

2.3.2. Optimized VBM—We employed the optimized VBM approach as detailed in Good et al 2001, using the above templates. To minimize mis-segmentation error, normalization was performed using the segmented GM and WM images. Original structural MRI images were segmented in native space and the resulting gray and white matter images then spatially

normalized to gray and white matter templates respectively to derive the optimized normalization parameters. These parameters were then applied to the whole-brain structural images in native space prior to a new segmentation (Good et al 2001; Mechelli et al., 2005).

We examined modulated and unmodulated voxel values in the segmented images. Modulation (Good et al., 2001) retains the absolute GM volume (GMV) post-normalization, whereas unmodulated data tests for regional differences in GM concentration (GMC; Good et al., 2001). Automated measures of whole brain tissue volumes for each subject were combined to obtain a measure of total intracranial volume (TIV).

2.4. Statistical Analyses

Comparisons were performed using an Analysis of Covariance (ANCOVA) model that included age, gender, site and TIV as covariates. We examined GMC differences bi-directionally for Controls versus Schizophrenia. The resulting set of voxels from each contrast represents a t-statistic map (SPM-t). SPM-t maps were thresholded for the main group comparison at $p < 0.05$ and corrected for multiple comparisons using the family wise error rate (FWE).

Coordinates of the most significantly different voxels were transformed from the MNI system to Talairach standard space (Talairach and Tournoux, 1998) using a MATLAB conversion program written by Matthew Brett (MRC Cognition and Brain Sciences Unit, England). Coordinates were then entered into the Talairach Daemon (Lancaster et al., 2000) to localize results.

To validate our study further, we investigated the main effects of site/location using only controls, by modeling only the 3 main (large) groups (JHU, WPIC and MPRC), excluding the smallest group (IOP) which contained significantly fewer subject numbers and used slightly different acquisition parameters. This analysis used an ANCOVA controlling for gender. An omnibus F-contrast examined any main effect of site. Additionally, multiple post-hoc t-tests (all combinations) were carried out and all resulting t-contrasts pooled in a null conjunction analysis at a threshold of $p<0.05$ FWE corrected for multiple comparisons, to reveal common gray matter differences between sites.

3. Results

3.1. Optimized GMC

In the whole sample, numerous regions showed significantly ($p<0.05$ FWE Corrected, $t = 5.28$) lower GMC in patients versus controls (Figure 1). Table 2 details relative volumes and Talairach coordinates of the significant areas. No region showed a significantly higher GMC in patients when corrected for multiple comparisons.

The whole 400-subject sample was divided by scanner location to examine differences within sub-groups. Groups were demographically matched across each site (Table 1). JHU subjects (133 SZ, 136 HC) comprised the majority of subjects, and accordingly displayed GMC differences similar to those found in the entire sample. Volumes and coordinates of regions showing significantly ($p<0.001$ FDR corrected, $t = 3.84$) lower GMC in JHU patients, relative to JHU healthy controls, are listed in Table 3. No region showed higher GMC in patients when corrected for multiple comparisons. Even when analyses were thresholded at the $p<0.001$ uncorrected level, in this large sample, we did not find increased GMC in any subcortical nuclei. Clusters found in the JHU sample that were also found in the complete sample were all smaller in volume.

Comparisons were also contrasted within the smaller samples from each site. Results from the MPRC scans were detailed in Giuliani, et al 2005. MPRC schizophrenia patients demonstrated ($p<0.001$ FDR corrected, $t = 3.84$) lower GMC in several regions as detailed in table 3). No region showed a significantly higher GMC in patients in the MPRC sample at this threshold. In the WPIC sample, at $p<0.001$ FDR corrected, patients had lower GMC in multiple cortical regions (See Table 3). No regions contained significantly higher GMC in schizophrenia patients. Due to the small number of images collected at the IOP (N=8, 11), the data were not analyzed individually.

3.2. Optimized GMV

In a whole sample voxel-by-voxel contrast, corrected for multiple comparisons, no regions showed ($p<0.05$, FWE Corrected) smaller GMV in schizophrenia.

As GMV results replicated the GMC pattern at lesser statistical significance, we investigated the impact of the additional modulation step. By calculating the mean of both groups using both optimized VBM methods (Figure 2), it is apparent that both methods reveal the same pattern of less GM in patients in the frontal, temporal, and subcortical/limbic regions, and more GM in the occipital and bordering ventricular regions. Calculating the standard deviation by group demonstrated that the images from patients with schizophrenia had more variance than healthy controls.

3.3. Main effect of Site

Examining main effect of site in controls revealed GMC differences in a small number of brain regions; however this location and pattern of GM difference (Figure 3 - shown in green) had minimal spatial overlap with our main effect of GM reductions in patients (Figure 3 – shown in orange), emphasizing that main effect of site had little impact on the latter findings. Table 2 also illustrates an approximate quantitative estimate of percentage overlap in suprathreshold voxels in these areas. Additionally, the evaluation of GMC differences across sites using a conjunction analysis (Etgen et al., 2005) revealed no significant voxels at the $p<0.05$ FWE corrected threshold.

Multiple brain imaging studies indicate widespread gray matter volume abnormalities in schizophrenia. Since 1999, almost 30 studies surveying the whole brain using VBM in schizophrenia; have found less GM in fronto-temporal regions, as summarized in Table 4. However, even with such an automatic method, studies disagree. The sample size of 200 patients and 200 matched controls makes the current VBM study of GM changes in schizophrenia the largest to date.

Our results complement previous ROI and VBM research in documenting less frontal, parietal, temporal, and sub-cortical GM reductions in schizophrenia. The main effects contrast found lower GMC in all published regions, plus areas including the superior parietal lobule, caudate, rectal gyrus, and transverse temporal gyrus. The only region previously documented as containing less GMV in schizophrenia undetected in our analyses was hippocampus, possibly because the peak difference in medial temporal lobe lies in the parahippocampal gyrus, only extending into the hippocampus proper at lower thresholds. Furthermore, GM changes in smaller sub-cortical structures, e.g. hippocampus, are harder to detect using VBM due to inherent problems in normalization and smoothing (Bookstein, 2001; McIntosh et al., 2004).

The most notable difference in our findings compared to previous studies is the larger number of regions we characterized as containing less GM in schizophrenia. This is not explained by differences in significance thresholds, as our p-value of $p<0.05$ corrected for multiple comparisons (FWE) is very stringent. One explanation is sample size. Another is

methodological differences in the implementation of VBM. We addressed the first question by amassing the largest number of patients and matched controls to date. Increasing subject numbers also increases statistical power. The next largest VBM study, performed by Hulshoff Pol et al., 2002, at a threshold of $p<0.05$ corrected for multiple comparisons ($|t|> 5.0$), schizophrenia patients had less GM in several temporal lobe areas, but few additional significant findings. In contrast to our data, however, that study did not capture GM differences in several critical areas such as the superior, middle, inferior frontal gyri, parahippocampus, amygdala and inferior parietal lobule, (See Table 4).

4. Discussion

4.1. Methodology

Our main methodological strength is the use of optimized VBM, namely the normalization of GM segments to a study-specific template. This ensures the reflection of GM distribution found within the study cohort, accounts for any data inhomogeneities due to scanner differences used, and ensures a minimal warping is required for coregistration. Also, normalization of the GM segments to the study-specific GM template reduces erroneous inclusion of missegmented non-brain voxels.

As our data was collected at four different sites, we tested robustly for scanner differences by: 1) Using a study-specific template to minimize effects of using data from four sites. 2) Accounting for confounding variables such as gender, location, age, and total intracranial volume. 3) Accessing a main effect of site to look at any GM differences that existed across scanners. 4) Using conjunction analysis to verify homogeneity of GM differences across sites. The decision to use only the healthy subjects' images to create the templates was supported by an ad hoc analysis of the data using a template from all 400 subjects, where results did not differ significantly from those reported. The normalization procedures, although highly reliable, render the VBM process less sensitive to group differences in shape or gray-white matter differentiation than previous ROI methods, and may misregister anatomical structures (Ashburner and Friston, 2001; Bookstein, 2001). The removal of global size differences in the normalization process is a caveat in all VBM studies, especially if brain atrophy is documented.

Several studies (Keller et al., 2004) have explored modulation to extend and possibly improve optimized VBM results. Comparing modulated and non-modulated VBM results, Keller et al. (2004) found more regions of GM loss using VBM of GMV than GMC, concluding that optimized VBM of GMV was more accurate to assess differences in regional brain volume. We found similar areas of lower GMV in patients, albeit less significant than the GMC results (Figure 2), due to increased within-group variance of patients' GM volumes. The multiplication by Jacobian determinants accounts for varied GM partitions and decreases statistical power.

4.2. This sample

The results from the whole sample and the individual site subsamples resembled each other except in parietal, occipital and limbic sub-regions, which we discuss by site. As two thirds of the main sample consisted of scans collected at JHU, a contrast of only those controls and patients should elicit GM differences in the majority of the same regions as the main effects analyses. Schizophrenia patients demonstrated significantly lower GMC in all areas seen in the main effects analysis with few exceptions discussed here (Table 3). All regions exhibiting differences in both the main effects and JHU samples were smaller in volume in the latter, consistent with our hypothesis that these regions would be less significant due to the smaller sample size of the JHU group.

However, (Table 3) additional JHU GMC differences that were insignificant or smaller in volume in the main effects contrast were noted. Most such areas were small in volume, and were not very significant.

It is impossible to tell whether sites with only chronic patients (MPRC) or only first episode unmedicated patients (WPIC) show differences due to illness stage or medication effects, or both. Cingulate gyrus, thalamus, middle temporal gyrus and transverse temporal gyrus differed from controls in chronic, but not first episode patients, consistent with the progression of GM changes seen in first episode patients followed longitudinally (Nakamura et al., 2007). An additional caveat of the study is the influence of former substance dependence (greater than 12 months) on any gray matter volume changes.

While the purpose of this study was not to examine between-site differences, we saw similar patterns of less GMC in schizophrenia within each of the sub-samples. The location of GMC differences varied slightly by site, as shown in Table 3, but all three sub-samples demonstrate significantly lower GMC in patients in most HASC regions. The other difference between samples is that of statistical significance, due to different sample sizes. The additive properties of these separate samples suggest benefit in combining images from several scanners. By using groups from Baltimore, Pittsburgh and London we account for unique subject-selection, geographical, and scanner-related variation. Interestingly, data from two sites within the city of Baltimore yielded different results, demonstrating that even combining geographically similar samples results in a more statistically powerful and generalizable sample.

4.3. Conclusion

We present the largest VBM study to date investigating GM in schizophrenia. By increasing subject numbers and using optimized VBM methods, we observed more and larger regions containing less GMC in schizophrenia than prior published studies. Also, we demonstrated that modulation of VBM results, converting GMC to GMV, did not improve our data. Regardless, these results suggest that VBM analyses of schizophrenia are greatly enhanced by using large, representative sample.

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References

Ananth H, Popescu I, Critchley HD, Good CD, Frackowiak RS, Dolan RJ. Cortical and subcortical gray matter abnormalities in schizophrenia determined through structural magnetic resonance imaging with optimized volumetric voxel-based morphometry. Am J Psychiatry 2002;159:1497–1505. [PubMed: 12202269]

Antonova E, Sharma T, Morris R, Kumari V. The relationship between brain structure and neurocognition in schizophrenia: a selective review. Schizophr Res 2004;70:117–145. [PubMed: 15329292]

Ashburner J, Friston KJ. Voxel-based morphometry--the methods. Neuroimage 2000;11:805–821. [PubMed: 10860804]

Ashburner J, Friston KJ. Why voxel-based morphometry should be used. Neuroimage 2001;14:1238–1243. [PubMed: 11707080]

Baumann B, Bogerts B. The pathomorphology of schizophrenia and mood disorders. similarities and differences. Schizophr Res 1999;39:141–148. [PubMed: 10507525]discussion 162

Buchanan RW, Francis A, Arango C, et al. Morphometric assessment of the heteromodal association cortex in schizophrenia. Am J Psychiatry 2004;161:322–331. [PubMed: 14754782]

Bookstein FL. "Voxel-based morphometry" should not be used with imperfectly registered images. Neuroimage 2001;14:1454–1462. [PubMed: 11707101]

Etgen T, Draganski B, Ilg C, et al. Bilateral thalamic gray matter changes in patients with restless legs syndrome. Neuroimage 2005;24:1242–1247. [PubMed: 15670702]

Falkai P, Vogeley K, Maier W. Structural brain changes in patients with schizophrenic psychoses. From focal pathology to network disorder. Nervenarzt 2001;72:331–341. [PubMed: 11386143]

First, MB.; Spitzer, RL.; Gibbon, M.; Williams, JBW. Structural Clinical Interview for DSM-IV Axis Disorders (SCID-IV). New York, NY: Biometrics Research Department, New York State Psychiatric Institute; 1997.

Gaser C, Volz HP, Kiebel S, Riehemann S, Sauer H. Detecting structural changes in whole brain based on nonlinear deformations-application to schizophrenia research. Neuroimage 1999;10:107–113. [PubMed: 10417245]

Giuliani NR, Calhoun VD, Pearlson GD, Francis A, Buchanan RW. Voxel-based morphometry versus region of interest. a comparison of two methods for analyzing gray matter differences in schizophrenia. Schizophr Res 2005;74:135–147. [PubMed: 15721994]

Good CD, Johnsrude IS, Ashburner J, Henson RN, Friston KJ, Frackowiak RS. A voxel-based morphometric study of ageing in 465 normal adult human brains. Neuroimage 2001;14:21–36. [PubMed: 11525331]

Honea R, Crow TJ, Passingham D, Mackay CE. Regional deficits in brain volume in schizophrenia. a meta-analysis of voxel-based morphometry studies. Am J Psychiatry 2005;162:2233–2245. [PubMed: 16330585]

Hulshoff Pol HE, Schnack HG, Bertens MG, et al. Volume changes in gray matter in patients with schizophrenia. Am J Psychiatry 2002;159:244–250. [PubMed: 11823266]

Job DE, Whalley HC, McConnell S, Glabus M, Johnstone EC, Lawrie SM. Structural gray matter differences between first-episode schizophrenics and normal controls using voxel-based morphometry. Neuroimage 2002;17:880–889. [PubMed: 12377162]

Keller SS, Wilke M, Wieshmann UC, Sluming VA, Roberts N. Comparison of standard and optimized voxel-based morphometry for analysis of brain changes associated with temporal lobe epilepsy. Neuroimage 2004;23:860–868. [PubMed: 15528086]

Keshavan MS, Sanders RD, Sweeney JA, et al. Diagnostic specificity and neuroanatomical validity of neurological abnormalities in first-episode psychoses. Am J Psychiatry 2003;160:1298–1304. [PubMed: 12832245]

Kubicki M, Shenton ME, Salisbury DF, et al. Voxel-based morphometric analysis of gray matter in first episode schizophrenia. Neuroimage 2002;17:1711–1719. [PubMed: 12498745]

Lancaster JL, Woldorff MG, Parsons LM, et al. Automated Talairach atlas labels for functional brain mapping. Hum Brain Mapp 2000;10:120–131. [PubMed: 10912591]

McIntosh AM, Job DE, Moorhead TW, et al. Voxel-based morphometry of patients with schizophrenia or bipolar disorder and their unaffected relatives. Biol Psychiatry 2004;56:544–552. [PubMed: 15476683]

Moorhead TW, Job DE, Whalley HC, Sanderson TL, Johnstone EC, Lawrie SM. Voxel-based morphometry of comorbid schizophrenia and learning disability. analyses in normalized and native spaces using parametric and nonparametric statistical methods. Neuroimage 2004;22:188–202. [PubMed: 15110009]

Mechelli A, Price CJ, Ashburner J, Friston KJ. Voxel-Based Morphometry of the Human Brain. Methods and Applications. Current Medical Imaging Reviews 2005:105–113.(9

Mesulam, MM. Principles of Behavioral and Cognitive Neurology. New York, NY: Oxford University Press; 2004.

Nakamura M, Salisbury DF, Hirayasu Y, et al. Neocortical Gray Matter Volume in First-Episode Schizophrenia and First-Episode Affective Psychosis. A Cross-Sectional and Longitudinal MRI Study. Biol Psychiatry 2007;62:773–783. [PubMed: 17586477]

Paillere-Martinot M, Caclin A, Artiges E, et al. Cerebral gray and white matter reductions and clinical correlates in patients with early onset schizophrenia. Schizophr Res 2001;50:19–26. [PubMed: 11378311]

Pearlson GD, Petty RG, Ross CA, Tien AY. Schizophrenia. a disease of heteromodal association cortex? Neuropsychopharmacology 1996;14:1–17. [PubMed: 8719025]

Talairach, J.; Tournoux, P. Co-planar Stereotactic Atlas of the Human Brain. 3-Dimensional Proportional System - an Approach to Cerebral Imaging. New York, NY: Thieme Medical Publishers; 1988.

Schlaepfer TE, Harris GJ, Tien AY, et al. Decreased regional cortical gray matter volume in schizophrenia. Am J Psychiatry 1994;151:842–848. [PubMed: 8184992]

Schretlen DJ, Munro CA, Anthony JC, Pearlson GD. Examining the range of normal intraindividual variability in neuropsychological test performance. J Int Neuropsychol Soc 2003;9:864–870. [PubMed: 14632245]

Shenton ME, Dickey CC, Frumin M, McCarley RW. A review of MRI findings in schizophrenia. Schizophr Res 2001;49:1–52. [PubMed: 11343862]

Sigmundsson T, Suckling J, Maier M, et al. Structural abnormalities in frontal, temporal, and limbic regions and interconnecting white matter tracts in schizophrenic patients with prominent negative symptoms. Am J Psychiatry 2001;158:234–243. [PubMed: 11156806]

Sowell ER, Levitt J, Thompson PM, et al. Brain abnormalities in early-onset schizophrenia spectrum disorder observed with statistical parametric mapping of structural magnetic resonance images. Am J Psychiatry 2000;157:1475–1484. [PubMed: 10964865]

Spitzer, RL.; Williams, JBW.; Gibbon, M.; First, MB. Structured Clinical Interview for DSM-III-R-Patient Version (SCID-P), 5/1/89. New York, NY: Biometrics Research Department, New York State Psychiatric Institute; 1989.

Suzuki M, Nohara S, Hagino H, et al. Regional changes in brain gray and white matter in patients with schizophrenia demonstrated with voxel-based analysis of MRI. Schizophr Res 2002;55:41–54. [PubMed: 11955962]

Wilke M, Kaufmann C, Grabner A, Putz B, Wetter TC, Auer DP. Gray matter-changes and correlates of disease severity in schizophrenia. a statistical parametric mapping study. Neuroimage 2001;13:814–824. [PubMed: 11304078]

Wright IC, Ellison ZR, Sharma T, Friston KJ, Murray RM, McGuire PK. Mapping of grey matter changes in schizophrenia. Schizophr Res 1999;35:1–14. [PubMed: 9988836]

Wright IC, Rabe-Hesketh S, Woodruff PW, David AS, Murray RM, Bullmore ET. Meta-analysis of regional brain volumes in schizophrenia. Am J Psychiatry 2000;157:16–25. [PubMed: 10618008]

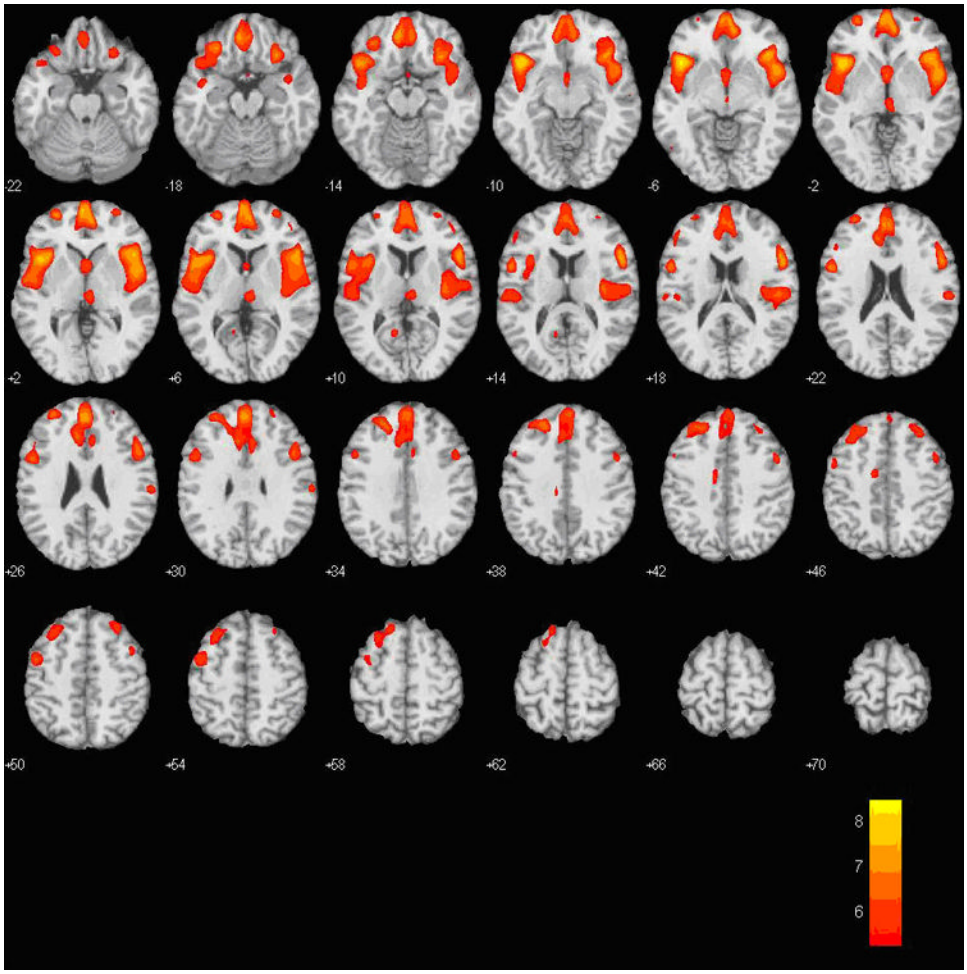

Figure 1.
Main effect group map with lower GMC (FWE corrected $p<0.05$, $t=5.28$) in schizophrenia patients relative to healthy controls.

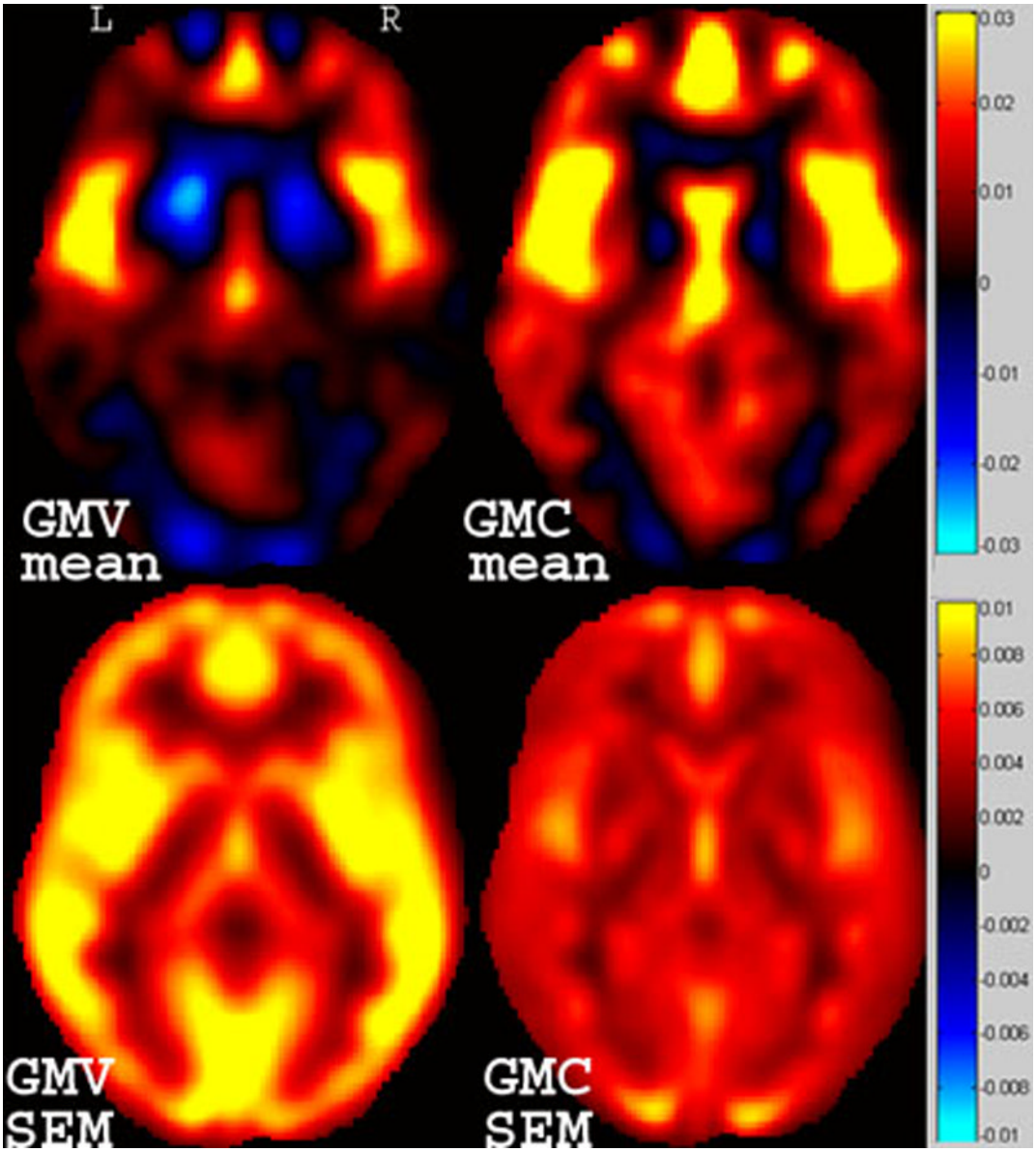

Figure 2.

Direct comparison of GMV and GMC results from the control > patient contrast. Areas in red contain more GM in control subjects, areas in blue contain more GM in schizophrenia patients. One slice from each GMC, GMV, mean and standard error of the mean (SEM) displayed. The GMC contrast has a higher mean and lower SEM than the GMV contrast, which corresponds to decreased statistical power of the latter.

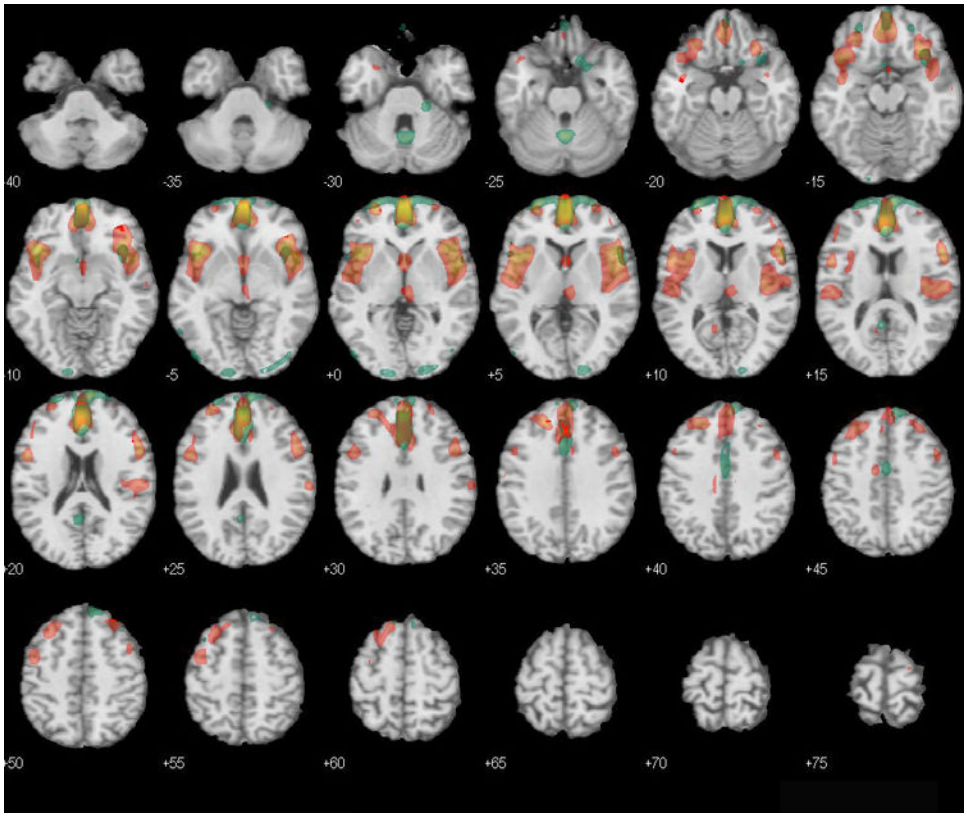

Figure 3.
Simultaneous overlay of GM concentration differences between the three major scanner sites (Displayed in green at $p < 0.05$, $F = 18.3$, FWE corrected for multiple comparisons.) and diagnosis (Displayed in orange at $p<0.05$ FWE corrected).

Table 1

Demographic data of participants included in the study, by scanner location.

*(1=male, 2=female)

Site	HEALTHY			SCHIZOPHRENIA				Age		Sex	
	N	Age (Mean ± Stdev)	Sex (M/F)	N	Age (Mean ± Stdev)	Sex (M/F)	Diagnosis (First Episode/Chronic)	t-score	p value	Chi square	p value
JHU	136	41.835 ± 16.22	67/69	133	41.579 ± 12.60	70/63	16(drug free)/117	0.14	0.88	0.18	0.67
MPRC	34	42.54 ± 6.88	17/17	34	41.318 ± 5.33	24/10	0/34	0.81	0.41	2.21	0.14
IOP	9	35.667 ± 7.26	4/5	11	41.091 ± 8.80	4/7	0/11	−1.47	0.15	0.13	0.71
WPIC	21	26.238 ± 7.49	13/8	22	25.091 ± 7.01	14/8	22 (treatment naïve)/0	0.51	0.3	0.01	0.9
TOTAL	**200**	**40.04 ± 14.77**	**101/99**	**200**	**39.694 ± 12.06**	**112/88**	**38/162**	**0.25**	**0.39**	**1.01**	**0.31**

Table 2

Areas with lower GMC in patients relative to controls: (FWE corrected p<0.05, t= 5.28)

Whole Sample, GMC: A summary of areas detected in the main effects analysis by diagnosis (controls > patients) along with their Talairach coordinates, volume and maximum t-value and its coordinate at a corrected p<0.05 (FWE, t=5.28). For all tables, each volume listed is the size of the cluster of contiguous voxels above a given threshold in each area. Also provided are the extent of GMC differences overlap between main effect of diagnosis and site.

Regions	Brodmann Areas	L (Vol CC)	Max T (x, y, z)	R (Vol CC)	Max T (x, y, z)	Percentage Overlap	
						L	R
Inferior Frontal Gyrus*	47, 45, 44, 46, 11, 13	8.2	8.3(−42,19,−7)	10.6	7.6(46,18,2)	3.66	1.89
Medial Frontal Gyrus*	10, 9, 11, 32, 6, 8	6.8	7.5(−3,60,−4)	8.5	7.4(3,60,−4)	14.70	8.23
Insula	47,13, 22, 40	6.9	7.9(−42,17,−2)	6.7	7.3(43,16,2)		
Superior Temporal Gyrus*	22, 38, 13, 42, 41	4.8	7.4(−46,13,−7)	5.5	7.5(49,4,1)	6.25	1.82
Middle Frontal Gyrus*	11, 10, 46, 9, 6, 8	6	7.0(−28,31,−17)	4.1	6.5(50,23,22)	6.67	9.76
Superior Frontal Gyrus*	10, 9, 8, 6	5.8	7.6(−3,61,−2)	2	7.4(3,61,−2)	25.86	60
Anterior Cingulate*	10, 32, 25, 42, 24	2.8	7.1(−3,55,−1)	2.6	7.3(6,54,−1)	17.86	15.38
Precentral Gyrus	44,6, 13, 43, 42	2.5	7.2(−50,11,6)	2.1	7.5(50,18,6)		
Postcentral Gyrus	43, 2, 1, 3, 40	0.5	6.0(−53,−18,15)	1.8	6.5(52,−17,17)		
Cingulate Gyrus*	32, 24	1.4	6.2(−6,30,26)	0.6	5.9(7,20,27)	21.43	16.67
Transverse Temporal Gyrus	41, 42	0.6	6.1(−50,−20,13)	0.6	6.1(48,−17,13)		
Thalamus	Medial Dorsal Nucleus, Pulvinar, Mammillary Body	0	NS	0.9	6.1(6,−19,4)		
Caudate	Caudate Head	0.1	5.6(−4,9,0)	0.4	6.1(4,9,0)		
Orbital Gyrus	11	0.3	6.5(−4,46,−19)	0.1	6.1(3,43,−19)		
Posterior Cingulate	23	0.4	5.8(−10,−53,12)	0	NS		
Rectal Gyrus	11	0.1	6.3(−4,37,−20)	0.1	6.1(1,37,−20)		
Subcallosal Gyrus	25	0	NS	0.1	5.5(3,7,−14)		
Middle Temporal Gyrus	21	0.1	5.3(−52,0,−24)	0.1	5.4(62,−11,−11)		
Inferior Parietal Lobule	39	0	NS	0.1	5.5(65,−22,26)		
Inferior Temporal Gyrus	19	0.1	5.4(−52,−61,−2)	0	NS		
Uncus	28	0.1	5.4(−24,7,−26)	0	NS		
Middle Occipital Gyrus	19	0.1	5.3(−52,−61,−4)	0	NS		

* Regions where GMC differences due to effect of site and diagnosis both overlap each other.

Table 3

By Site, GMC: A summary of areas detected in the JHU, MPRC and WPIC sub-sample analyses by diagnosis (controls > patients) along with their Talairach coordinates, volume and maximum t-value and its coordinate at a corrected p<0.001 (FDR, t=3.84).

	JHU SUBJECTS				MPRC SUBJECTS				WPIC SUBJECTS			
	Vol (cc)		Max T (x,y,z)		Vol (cc)		Max T (x,y,z)		Vol (cc)		Max T (x,y,z)	
Brain Region	**L**	**R**	**L**	**R**	**L**	**R**	**L**	**R**	**L**	**R**	**L**	**R**
Inferior Frontal Gyrus	12.6	15.9	6.8(−9,40,−16)	6.4(30,27,−15)	2.6	2.8	4.9(−43,9,29)	5.1(33,20,−16)	1.8	3.4	3.1(−52,19,−3)	**3.3(50,25,11)**
Middle Frontal Gyrus	9.9	9.4	5.7(−24,27,−18)	6.1(30,33,−13)	1.3	0.9	4.4(−43,15,28)	4.4(28,34,43)	2.7	0.9	3.7(−58,52,−13)	**3.1(27,38,−21)**
Precentral Gyrus	4	2.3	5.2(−48,2,48)	5.0(49,18,6)	0.7	0.6	4.7(−50,7,13)	4.6(53,9,4)	1.7	0.3	3.0(−53,−5,24)	**2.8(50,16,9)**
Insula	4.3	4.6	5.3(−39,16,−1)	5.0(40,19,2)	1.4	1	4.9(−42,2,−11)	4.2(40,11,−9)	2.7	1.7	3.2(−33,13,8)	**3.3(36,−12,13)**
Superior Temporal Gyrus	7.2	5.4	5.6(−45,15,−11)	5.2(48,14,−7)	1.7	2.8	5.2(−42,−1,−14)	4.8(53,6,2)	0.8	0	2.7(−64,−23,12)	**N.S.**
Medial Frontal Gyrus	12.5	12.4	7.0(−7,43,−16)	6.1(7,49,−4)	2.4	4.5	5.3(−6,62,−12)	6.5(7,64,0)	0.9	1.7	4.4(−7,70,−5)	**3.5(4,72,−9)**
Superior Frontal Gyrus	7.4	4.1	5.6(−18,39,30)	5.8(6,54,−1)	3.2	3.9	5.2(−6,62,−9)	6.3(7,62,−3)	4	3.4	4.9(−12,73,−2)	**3.3(25,40,−23)**
Claustrum	0.5	0.5	4.7(−34,15,2)	4.5(36,−8,11)					1.5	0.7	3.3(−33,−14,15)	**3.2(34,−15,12)**
Anterior Cingulate	4.2	2.1	5.9(−3,54,−1)	6.0(6,51,−1)	0.8	1	5.0(−4,5,−8)	4.9(4,5,−7)	0.4	0.6	2.9(−1,13,−1)	**2.9(1,13,−1)**
Postcentral Gyrus	1.1	2.2	4.4(−53,−17,15)	5.0(53,−18,19)	0	0.2	N.S.	4.1(64,−19,31)	0.2	0.3	2.7(−53,−8,20)	**2.7(25,−43,70)**
Hypothal./Substantia Nigra					0.2	0.8	4.8(−6,8,−8)	5.0(6,5,−10)				
Rectal Gyrus	1	0.6	5.9(−6,37,−20)	5.3(0,37,−20)								
Cingulate Gyrus	3.4	0.9	5.5(−12,−4,40)	4.3(10,−40,37)	0.2	1.1	4.0(−9,−17,35)	5.1(12,−13,37)				
Orbital Gyrus	0.9	0.4	6.5(−6,43,−19)	5.4(0,43,−19)					0	0.1	N.S.	**2.8(22,38,−25)**
Thalamus	0.1	2.1	4.0(−9,−14,9)	4.7(13,−18,9)	0.8	1.2	4.8(−1,−19,8)	4.9(0,−17,4)				
Transverse Temporal Gyrus	0.9	0.4	4.4(−50,−20,12)	4.3(58,−12,14)	0	0.1	N.S.	4.0(55,−20,12)				
Caudate					1	1.5	4.9(−4,8,−5)	4.8(4,9,−4)	0.5	0.6	2.9(−3,15,−1)	**2.9(3,15,1)**
Posterior Cingulate	0.8	0	4.5(−10,−55,11)	N.S.					0.3	0.1	2.8(−18,−55,17)	**2.7(24,−54,18)**
Inferior Temporal Gyrus	2	0.3	4.9(−52,−61,−2)	4.2(31,−6,−35)	0	0.5	4.1(−43,−4,−16)	4.5(64,−13,−23)	0.5	0.5	3.4(−55,−26,−34)	**3.2(56,−25,−33)**
Middle Temporal Gyrus	1.6	0.7	5.1(−55,−1,−23)	4.5(62,−11,−11)	0	0	4.0(−43,1,−19)	3.9(65,−15,−14)				
Inferior Parietal Lobule	0.2	0.1	4.4(−53,−45,23)	4.3(56,−19,22)					0	0.1	N.S.	**2.5(65,−40,45)**
Middle Occipital Gyrus	0.3	0	5.1(−52,−61,−4)	N.S.								
Amygdala	0.6	0.2	4.2(−19,−31,−10)	4.2(25,−28,−4)								
Fusiform Gyrus	0.4	0	4.8(−40,−5,−19)	N.S.	0	0	N.S.	3.9(61,−11,−25)	0.6	0	3.4(−56,−26,−31)	**2.5(58,−22,−30)**
Supramarginal Gyrus	0.4	0.1	4.3(−53,−46,20)	4.1(52,−48,25)								
Subcallosal Gyrus					0.8	0.8	4.8(−4,7,−10)	5.0(4,8,−14)				
Parahippocampal Gyrus					0.1	0.1	3.9(−10,2,−20)	4.0(10,−1,−21)				
Precuneus	0.3	1.4	4.1(−10,−48,40)	4.7(12,−63,45)					0.1	0.1	2.7(−21,−62,20)	**2.6(12,−81,7)**
Lingual Gyrus	0.1	0.3	4.1(−30,−57,−2)	4.4(24,−70,−4)								
Uncus	0.5	0.6	4.7(−27,9,−29)	4.4(28,−6,−35)	0.1	0.6	4.1(−15,6,−19)	4.2(21,8,−24)				
Lateral Geniculum Body	0.1	0.1	5.8(−1,57,1)	4.2(24,−25,−1)								

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Table 4

Summary of regions with significantly less GM in schizophrenia patients than healthy controls by scanner and study (1 = current study, all subjects; 2 = current study, JHU subsample; 3 = current study, MPRC subsample; 4 = Moorhead, 2004; 5 = McIntosh, 2004; 6 = Ananth, 2003; 7 = Giuliani, 2004; 8 = Suzuki, 2002; 9 = Palliere-Marinot, 2001; 10 = Hulshoff Pol, 2001; 11 = Kubicki, 2002; 12 = Wilke, 2001; 13 = Antonova, 2003; 14 = Wright, 1999; 15 = Job, 2002; 16 = Gaser, 1999; 17 = WPIC subsample)

Brain Region	Current study site	Prior Study
Superior Frontal Gyrus	1,2,3,17	**4,6,7,8,16**
Middle Frontal Gyrus	1,2,3,17	**5,7,8,11,14,16**
Medial Frontal Gyrus	1,2,3,17	**6,7,9,12,15**
Inferior Frontal Gyrus	1,2,3,17	**5,6,7,8,12**
Orbital Gyrus	1,2,17	**6,10,12**
Rectal Gyrus	1,2	
Precentral Gyrus	1,2,3,17	**6,7,9,13,16**
Subcallosal Gyrus	1,3	**7**
Postcentral Gyrus	1,2,3,17	**6,7,15**
Insula	1,2,3,17	**7,9,10,11,12,14**
Superior Temporal Gyrus	1,2,3,17	**4,7,8,10,11,12,13,14,16**
Middle Temporal Gyrus	1,2,3	**7,10,12,13,15**
Inferior Temporal Gyrus	1,2,3,17	**4,6,7,10,13**
Transverse Temporal Gyrus	1,2,3	**7**
Parahippocampal Gyrus	1,3	**4,5,7,9,13,15**
Hippocampus		**8,10,11**
Amygdala	1,2	**10,14,15**
Uncus	2,3	**7,15**
Anterior Cingulate	1,2,3,17	**7,8,9,11,15**
Posterior Cingulate	1,2,17	**7,10**
Superior Parietal Lobule	1	
Inferior Parietal Lobule	1,2,17	**6,11**
Supramarginal Gyrus	1,2	
Middle Occipital Gyrus	1,2	**6**
Fusiform Gyrus	1,2,3,17	**6,7,9**
Lingual Gyrus	1,2	**16**
Precuneus	1,2	**10**
Cuneus	1	**4**
Caudate	1,3,17	**7**
Thalamus	1,2,3	**5,6,7,10,16**
Claustrum	1,2,3,17	**7**
Lateral Geniculum Body	2,3	**7**
Hypothalamus	1,3	**7**