Meta-Analysis of Gray Matter Anomalies in Schizophrenia: Application of Anatomic Likelihood Estimation and Network Analysis

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Background: Although structural neuroimaging methods have been widely used to study brain morphology in schizophrenia, synthesizing this literature has been difficult. With the increasing popularity of voxel-based morphometric (VBM) methods in which group differences are reported in standardized coordinates, it is possible to apply powerful meta-analytic techniques initially designed for functional neuroimaging. In this study, we performed a voxelwise, coordinate-based meta-analysis to better conceptualize the neuroanatomic correlates of schizophrenia.

Methods: Thirty-one peer-reviewed articles, with a total of 1195 patients with schizophrenia contrasted with 1262 healthy volunteers, were included in the meta-analysis. Coordinates from each article were used to create a statistical map that estimated the likelihood of between-group gray matter density differences at every brain voxel. These results were subsequently entered into a network analysis.

Results: Patients had reduced gray matter density relative to control subjects in a distributed network of regions, including bilateral insular cortex, anterior cingulate, left parahippocampal gyrus, left middle frontal gyrus, postcentral gyrus, and thalamus. Network analysis grouped these regions into four distinct networks that potentially represent different pathologic processes. Patients had increased gray matter density in striatal regions.

Conclusions: This study expands on previous meta-analyses of the neuroanatomy of schizophrenia by elucidating a series of brain networks disrupted by the illness. Because it is possible that these networks are influenced by independent etiologic factors, this work should foster more detailed neural models of the illness and focus research designed to discover the mechanisms of gray matter reduction in schizophrenia.

Key Words: Gray matter density, meta-analysis, network analysis, schizophrenia, voxel-based morphometry

Structural neuroimaging methods have been widely used to study brain morphology in schizophrenia, providing important information about possible pathophysiologic mechanisms of this debilitating illness. Since Johnstone and colleagues' (1) seminal findings of increased lateral ventricular size in patients with schizophrenia, more than 300 peer-reviewed articles have delineated the subtle neuroanatomic abnormalities in the illness. However, synthesizing this literature has been difficult given the variability of the patient populations studied, significant changes in imaging technologies, and inconsistencies in the image analysis methods employed between studies. Recently, a number of meta-analyses have attempted to overcome these limitations and quantify the neuroanatomic changes found in schizophrenia (2–5). Although these reviews address issues of sample selection (e.g., focusing on first episode patients; 2, 6) or variation in critical imaging parameters (e.g., computed tomography [CT] vs. magnetic resonance imaging [MRI], slice thickness; 7), the inferences that can be drawn from these reviews are restricted by differences in the image analysis procedures applied in individual studies.

The vast majority of brain morphology studies in schizophrenia use a region of interest (ROI) approach in which specific brain regions are either manually or automatically delineated on the basis of a set of operationalized procedures (8). Although ROI-based image analysis procedures are often robust, internally consistent, and advisable in some situations, they are less than optimal when attempting to systematically review a large neuroanatomic literature. Specifically, the procedures used to define particular brain regions differ dramatically between laboratories, making direct comparisons of reported results difficult. This issue is compounded when authors use dissimilar labels to describe the same brain area (9). Moreover, many manuscripts applying ROI methods to study brain changes in schizophrenia focus on a relatively small number of hypothesized brain regions, potentially biasing results in favor of studied regions and obscuring structural differences in nonhypothesized brain regions. Together these issues significantly reduce the benefit of conducting meta-analytic reviews of ROI-based neuroanatomic studies of schizophrenia (Supplement 1).

The past decade has seen the emergence of several new computational approaches to image analysis designed specifically to overcome the difficulties with ROI-based methods (10). Spurred by advances in differential geometry, Bayesian statistics, and by improved imaging acquisition methodology, these computational neuroanatomic methods are revolutionizing our ability to study brain morphology in vivo in clinical and healthy populations (11). The most popular of these novel tools is voxel-based morphometry (VBM), a procedure that involves spatially normalizing high-resolution neuroanatomic images into

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Received January 8, 2008; received March 12, 2008; accepted March 14, 2008.

0006-3223/08/$34.00
doi:10.1016/j.biopsych.2008.03.031

a common stereotactic space and conducting a voxelwise comparison of the local concentration (probability) of gray or white matter to determine group differences on the basis of these measures (12,13). Most investigators who employ VBM methods report between group gray or white matter density differences in standardized three-dimensional (3D) coordinates.

The practice of reporting brain locations as coordinates in stereotactic space is common in the functional neuroimaging literature (14), improving the generalizability of individual experiments and fueling the development of novel meta-analytic procedures (15). One such development, activation likelihood estimation (ALE), capitalizes on the nature of voxelwise studies by pooling 3D coordinates in stereotactic space from like studies, models each coordinate as a Gaussian distribution, and provides the probability of an event occurring at each brain voxel. Probability maps are then thresholded using common imaging methodologies such as permutation tests and false discovery rate. Unlike traditional meta-analyses that merge results from multiple studies to test for significance in pooled data (16), coordinate-based ALE meta-analyses search for locations of agreement among statistically significant effects (9,17). Another significant advantage of voxel-based methods is that because every location in the brain is included in the meta-analysis, it is possible to conduct innovative network analyses that dissociate large spatially distributed networks of brain regions into smaller, more homogeneous systems or subnets (18). In the context of functional neuroimaging, these subnets represent brain regions that are putatively engaged by similar cognitive demands. In anatomic studies, subnets may represent regions that are influenced by common etiologic or environmental factors.

In this study, we conducted a voxelwise, coordinate-based meta-analysis of neuroanatomic data to describe the gray matter density changes found in schizophrenia. The study expands on Honea and colleagues' 2005 (5) tabular meta-analysis of schizophrenia VBM studies by 1) applying a fully automated coordinate-based meta-analysis method, 2) performing a network analysis to further subdivide and characterize the findings, and 3) expanding the number of included studies from 15 to 31.

Methods and Materials

Literature Search and Selection

A comprehensive search for VBM studies investigating patients with schizophrenia was carried out with PubMed. Studies were included if they 1) reported whole-brain results in stereotactic (x, y, z) coordinates, 2) included patients with schizophrenia and healthy comparison subjects, and 3) followed, in general, the VBM protocols described by Ashburner and Friston (12) or Good and colleagues (13). Studies were excluded if they only reported brain changes over time (19,20) or included only individuals at high risk for, but not actually diagnosed with, schizophrenia (21). In addition, an article investigating the effects of antipsychotic treatment on the brain morphometry in schizophrenia was excluded (22), whereas another was excluded because all patients with schizophrenia had comorbid substance use disorders (23). To minimize the possibility of nonindependent observations, when studies with overlapping samples were considered, only the article with the largest sample was included. Thus our meta-analysis included 31 peer-reviewed articles with a total of 1195 patients with schizophrenia contrasted with 1262 healthy volunteers (Table 1).

In total, these articles included 379 foci of which 315 were included in the meta-analysis statistically comparing regions where healthy subjects had significantly higher gray matter density than patients. The remaining 64 foci were included in meta-analytic procedures examining the reverse contrast (patients > healthy subjects).

Table 1. Thirty-One Published Voxel-Based Morphometry Studies Including 1195 Patients with Schizophrenia Contrasted with 1262 Healthy Volunteers

Published Study	Patients with Schizophrenia	Healthy Subjects	Healthy > Patients	Patients > Healthy
Ananth *et al.,* 2002 (55)	20	20	X	
Antonova *et al.,* 2005 (56)	45	45	X	X
Bassitt *et al.,* 2007 (57)	50	30		X
Chua *et al.,* 2007 (58)	26	38	X	
García-Martí *et al.,* 2007 (59)	18	19	X	
Giuliani *et al.,* 2005 (60)	41	34	X	X
Ha *et al.,* 2004 (61)	35	35	X	X
Honea *et al.,* 2007 (62)	169	212	X	X
Hulshoff Pol *et al.,* 2001 (63)	159	158	X	X
Jayakumar *et al.,* 2005 (64)	18	18	X	
Job *et al.,* 2002 (65)	34	36	X	
Kasparek *et al.,* 2007 (66)	22	18	X	
Kawasaki *et al.,* 2004 (67)	25	50	X	X
Kawasaki *et al.,* 2007 (68)	30	30	X	
Kubicki *et al.,* 2002 (69)	16	18	X	
Marcelis *et al.,* 2003 (70)	31	27	X	X
McIntosh *et al.,* 2004 (71)	26	49		X
Moorhead *et al.,* 2004 (72)	25	29	X	
Neckelmann *et al.,* 2006 (73)	12	12	X	
Ohnishi *et al.,* 2006 (74)	47	76	X	
Paillere-Martinot *et al.,* 2001 (75)	20	20	X	X
Salgado-Pineda *et al.,* 2003 (76)	13	13	X	
Salgado-Pineda *et al.,* 2004 (77)	14	14	X	
Shapleske *et al.,* 2002 (78)	72	32	X	X
Sigmundsson *et al.,* 2001 (79)	27	27	X	X
Suzuki *et al.,* 2002 (80)	45	42	X	X
Whitford *et al.,* 2005 (81)	31	30	X	
Whitford *et al.,* 2006 (82)	41	47	X	X
Wilke *et al.,* 2001 (83)	48	48	X	X
Wright *et al.,* 1999 (84)	15	15	X	
Yamada *et al.,* 2007 (85)	20	20	X	
Total	1195	1262	29	15

Anatomical Likelihood Estimation Meta-Analysis Procedures

To meta-analyze VBM studies, the results from each individual experiment, represented as a set of coordinates in a standard stereotactic space, were combined with Anatomic Likelihood Estimation methods to identify areas of anatomy that were consistently implicated across studies. More specifically, coordinates of VBM foci were pooled to search for convergence in location via the implementation of GingerALE within the BrainMap database system (http://brainmap.org) (17,24). Upon entry into the database, the spatial normalization template (e.g., MNI305 or ICBM152) of each article was noted, and the coordi-

nates were automatically transformed to allow analysis using Talairach coordinates (25). Coordinates published in Montreal Neurological Institute (MNI) space were transformed to the Talairach coordinates using the icbm2tal algorithm (26), which has shown to provide improved fit over the mni2tal transform. Furthermore, coordinates from articles that employed the mni2tal transform were transformed back into MNI space and then into Talairach space via the icbm2tal algorithm. Included foci were blurred with a full width at half maximum (FWHM) of 12 mm, and the ALE statistic was computed for every voxel in the brain. Separate ALE maps were created for coordinates where healthy subjects had greater gray matter density than individuals with schizophrenia and where patients with schizophrenia had greater gray matter density than comparison subjects. Statistical significance was determined using a permutation test of randomly generated foci that was corrected for multiple comparisons. Five thousand permutations were computed using the same FWHM value (i.e., 12 mm) and the same number of foci (i.e., 315 or 64) used in computing the ALE values. The final ALE maps were thresholded at $p < .01$ (false discovery rate [FDR]-corrected) and clusters of less than 400 mm^3 were excluded. Although this study was restricted to gray matter, thresholded ALE maps are displayed on a reference image in Talairach space (27) to facilitate interpretation.

Fractional Similarity Network Analysis (FSNA)

Neumann and colleagues (28) developed a replicator-dynamics-based method for modeling interregional connectivity to isolate cortical networks commonly engaged together across studies. However, the replicator dynamics method is limited in that only the dominant subset of nodes in a network can be identified. To model every node in a complex network, Lancaster and colleagues (18) extended Neumann's technique with a binary pattern matching algorithm, creating fractional similarity network analysis (FSNA). FSNA identifies subordinate networks within a larger network by creating a co-occurrence matrix, in which each element indicates how often a given pair of regions is coactivated in a given study (28,29).

To expand on the basic meta-analysis in this study, FSNA was performed on ALE maps. The occurrence of each of the ALE

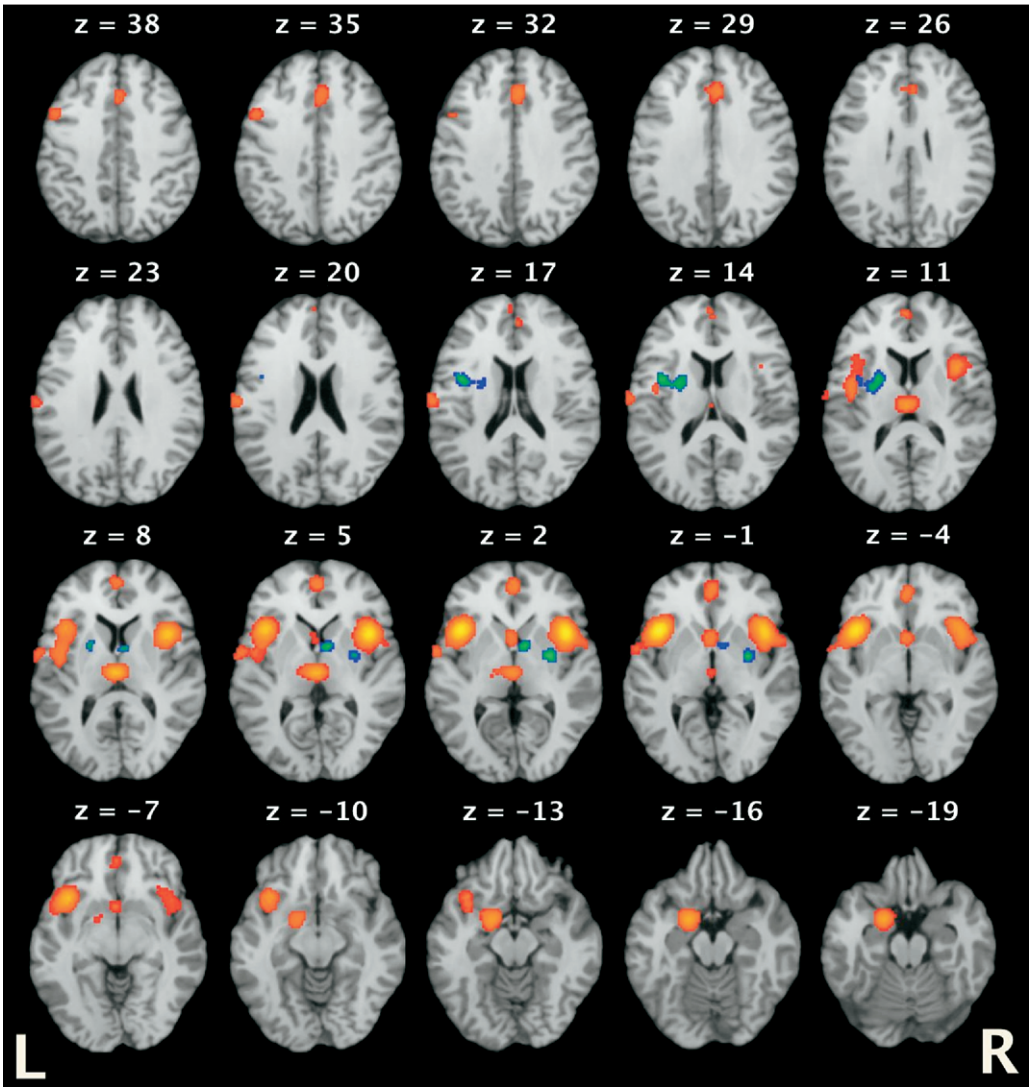

Figure 1. Results from an activation likelihood estimation meta analysis of 31 voxel-based morphometric studies investigating gray matter density changes in schizophrenia. Lighter grays represent areas of gray matter density decrease in patients with schizophrenia relative to healthy comparison subjects. Darker grays represent areas of increased gray matter density in patients with schizophrenia relative to comparison subjects.

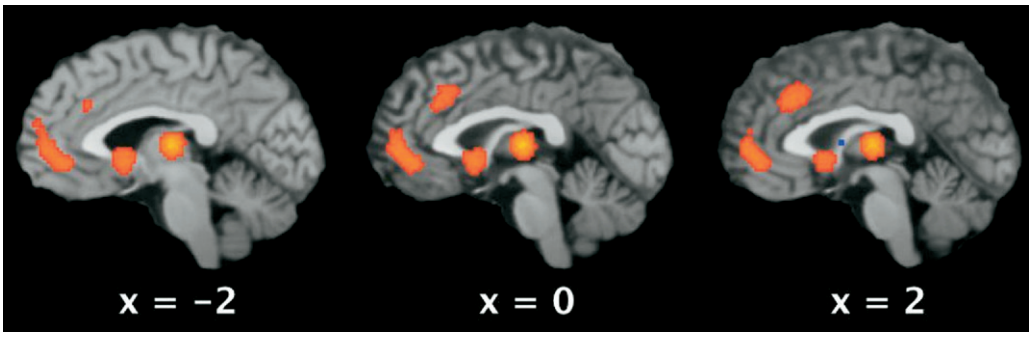

Figure 2. Three regions of anterior cingulate gyrus were found to have lower gray matter density in schizophrenia: dorsal, ventral, and subgenual. These regions include both the cognitive and affective regions of cingulate.

nodes in the included studies was noted, and the co-occurrence matrix was computed for all nodes, in all studies. FSNA was used to determine which nodes (brain regions) in the network formed subnetworks (subnets), using the simple S1 similarity coefficient to assess pattern similarity (18). The purpose of the FSNA analysis is to provide groups of regions or subnets that show comparable patterns across studies and may be influenced by similar factors of interest, such as an etiologic mechanism or sensitivity to medication effects.

Results

Healthy Comparison Subjects > Patients with Schizophrenia

Meta-analysis results are presented in Figures 1 and 2 and Table 2. Across studies, patients with schizophrenia had reduced gray matter density compared with healthy subjects in a network of nine brain regions. The largest cluster was centered on the left insular cortex (−40, 14, 0; Brodmann area [BA] 13). This region also included the left inferior frontal gyrus (BA 47), superior temporal gyrus (BA 22 and 38), and the precentral gyrus (BA 6 and 44).

A homologous, although more punctate, region was identified in right insular cortex (40, 10, 4; BA 13). This region included the inferior frontal gyrus (BA 47) but did not extend into the temporal lobe or the precentral gyrus. The third largest cluster was centered in the left parahippocampal gyrus (−18, −2, −16; BA 34) and extended to include the amygdala. Three midline regions were centered on the anterior cingulate gyrus (Figure 2): one dorsal (0, 48, 4; BA 32 and 10), one ventral (4, 26, 32; BA 32 and 6), and one subgenual (0, 6, −2). A midline thalamic (0, −20, 6) region was also identified, which presumably indicates bilateral thalamic alterations in schizophrenia. Additionally, an area of left postcentral gyrus (−62, −16, 18; BA 43) was also designated as being distinctly different between groups. Finally, patients with schizophrenia showed consistent gray matter density reductions in left middle frontal gyrus (−46, 10, 36; BA 9), an area putatively linked to executive functioning (30,31).

Table 2. Gray Matter Reductions in Schizophrenia Patients Relative to Healthy Comparison Subjects

Brain Region	Volume (mm^3)	Brodmann Area	Talairach Coordinate[a]	Maximum ALE Value
Left Insular Cortex	9336	13	−40, 14, 0	.026
Right Insular Cortex	6968	13	40, 10, 4	.026
Left Parahippocampal Gyrus	2504	34	−18, −2, −16	.018
Thalamus	2296	—	0, −20, 6	.020
Ventral Anterior Cingulate	1680	32	0, 48, 4	.013
Dorsal Anterior Cingulate	1400	32	4, 26, 32	.013
Subgenual Anterior Cingulate	968	25	0, 6, −2	.012
Left Postcentral Gyrus	608	43	−62, −16, 18	.012
Left Middle Frontal Gyrus	432	9	−46, 10, 36	.011

ALE, activation likelihood estimation.
[a]Talairach coordinate for the maximum ALE value.

Patients with Schizophrenia > Healthy Comparison Subjects

Of the 31 papers included in this review, 15 reported gray matter density increases in patients with schizophrenia relative to healthy comparison subjects (Table 1). Regions of increased gray matter density in schizophrenia were more discrete and smaller than areas of relative decrease. Across articles, three subcortical regions were consistently identified: left (volume 1248 mm^3; −38, 0, 16) and right (464 mm^3; 28, −6, 2) putamen (lentiform nucleus) and the right head of the caudate (424 mm^3; 8, 0, 4). The left putamen cluster extended into a portion of the insula (BA 13) that is just superior to areas of relative gray matter density decrease.

Fractional Similarity Network Analysis

Given that only three regions were identified in which patients with schizophrenia had greater gray matter density than comparison subjects, this contrast was not included in network analyses. For the ALE results identifying regions of reduced gray matter density in patients compared with healthy subjects, a binary co-occurrence matrix was computed with 29 columns (input studies) and 9 rows (ALE nodes). FSNA identified four subnets indicating that regions of gray matter density reduction in schizophrenia commonly co-occur across studies (Figure 3). The largest subnet included bilateral insular regions, the left parahippocampal area, and the left postcentral gyrus. The left middle frontal gyrus and ventral anterior cingulate were grouped into the second subnet. The third included the thalamic region and the dorsal anterior cingulate. The final subnet included only the subgenual cingulate.

Discussion

We performed a voxelwide, coordinate-based meta-analytic method on results from 31 VBM studies that contrasted the gray matter density of 1195 patients with schizophrenia with 1262 healthy comparison subjects. The results indicate that patients

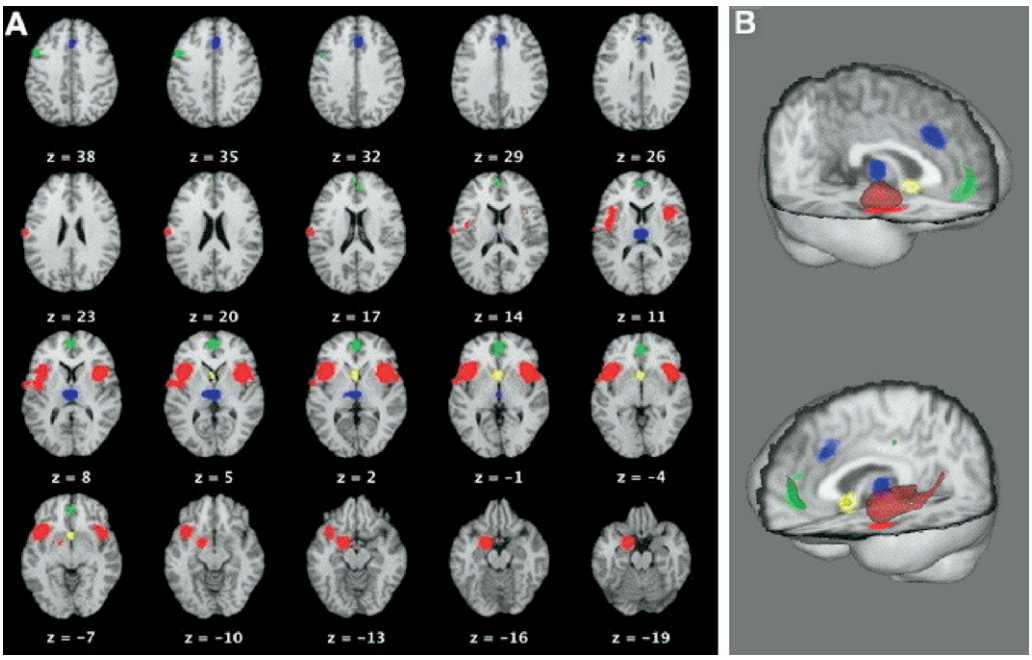

Figure 3. Fractional similarity network analysis parsed regions of gray matter density reduction in schizophrenia into four distinct subnets: bilateral insular cortex and left parahippocampal and left postcentral gyri; left middle frontal gyrus and ventral anterior cingulate; thalamus and dorsal anterior cingulate; and subgenual cingulate. **(A)** Two-dimensional views of these subnets; **(B)** three-dimensional rendering of these network components.

have reduced gray matter density relative to control subjects in a distributed network of regions, including bilateral insular cortex, anterior cingulate, left parahippocampal gyrus, middle frontal gyrus, postcentral gyrus, and thalamus. These regions were grouped into four distinct systems or subnets, each of which could reflect different aspects of the pathophysiology of schizophrenia, specific environmental influences, or factors that vary across studies. For example, grouping of gray matter density reductions in BA 9 and BA 32 may be associated with the cognitive control deficits that are putatively central to the manifestation of schizophrenia (32).

Three separate areas of the anterior cingulate gyrus were implicated in our analysis (Figure 2). These regions include both "affective" and "cognitive" portions of the anterior cingulate (33) and strengthen arguments for the importance of this gyrus in the pathology of schizophrenia (34). The network analysis placed each subregion of the anterior cingulate into separate subnets, suggesting that these regions may be influenced by different aspects of the etiology of schizophrenia or by differences in the implementations of VBM experiments (e.g., sample selection, sample size, imaging methods). Of these three regions, the subgenual finding has been reported least often. Upon closer inspection, we determined that this cluster was composed of coordinates from four separate studies and that these authors defined this location as subgenual cingulate (35), subcallosal gyrus (36,37), or left caudate (38). Although both the maximum value (0, 6, −2) and centroid (−1, 10, −6) of this cluster are within the subgenual cingulate, the actual resolution of our analysis does not allow for the level of parcellation needed to exclude definitively other proximal structures within the basal forebrain. The subgenual cingulate has been linked to mood disorders (39) and may be associated with the affective blunting commonly observed in schizophrenia (40–42).

Individuals with schizophrenia had higher gray mater density compared with control subjects in the striatum, specifically in the left and right putamen and in the right caudate. Increased striatal gray matter density may be associated with typical (3,43) or atypical (44,45) antipsychotic usage, with at least one article reporting enlarged caudate volume occurring in patients on olanzapine treatment (46). Although it is tempting to argue that findings of increased striatal gray matter density may be secondary antipsychotic usage, several investigators have not found this association (22,47). Only large-scale randomized controlled trials with longitudinal imaging can address this issue.

Although VBM is surprisingly well adapted for coordinate-based meta-analyses, the method does have limitations that should be considered when interpreting results. VBM analyses capture similar information as traditional region of interest methods (36,48–50), but they may overrepresent group differences in areas of high anatomic variability (50,51). Furthermore, they may be biased toward detecting highly localized group differences and biased against detecting group differences when these differences are spatially complex (52). The number of subjects included in analyses could significantly influence VBM results (53). Although in our meta-analysis we did not weight studies by the number of subjects included, we did not observe an obvious relationship between the sample size and the number of anatomic regions implicated in schizophrenia, with the exception that the study with the largest sample (54) was the only experiment to nominate all of the regions identified in the meta-analysis. Finally, variation in the exact image analysis methods applied in individual articles (e.g., the size of the smoothing kernel, significance-level or thresholding scheme, method for correcting for multiple comparisons, or the application of Jacobian modulations) likely influences findings. Because there is no standard VBM method and few studies directly compare analytic approaches when investigating schizophrenia, it is difficult to determine how specific choices affect results. Such variation significantly increases the need for replication across studies and, subsequently, the need for meta-analyses.

As with any meta-analytic method, the ALE technique is limited by the detail of the primary research articles. This is most apparent when investigators report a single midline coordinate for a cluster that includes both left and right regions. For example, although the thalamic cluster reported in our analysis is represented as a single midline region, inspection of the source manuscripts indicates that reduced gray matter density was observed in both the left and right thalamus and that authors tended to report a single coordinate for these overlapping regions. An additional aspect of this meta-analytic technique is that, as with functional neuroimaging methods, the procedure through which an ALE map is thresholded is somewhat arbitrary. Here we choose a conservative threshold of $p < .01$ after correcting for multiple comparisons. However, if we had chosen the more liberal threshold of $p < .05$, our results would have been similar to those reported with the exception of two additional brain areas: a right parahippocampal gyrus region (including amygdala) and a right middle frontal gyrus region (BA 9 and 8). Both of these regions are similar to, but smaller, than left hemisphere clusters that survived the more stringent thresholding. Thus, although our findings could support a left hemisphere model of schizophrenia, this interpretation may simply result from our choice of threshold rather than a true biological effect.

Although the application of brain function-location meta-analysis to anatomic rather than functional neuroimaging data is novel, the procedures are identical, and the conceptualization of results is straightforward. The use of voxelwise ALE methods in our study succinctly describes gray matter density changes in schizophrenia and may foster more detailed neural models of illness. Although it is unknown whether reduced gray matter density across the implicated regions leads to the cognitive fractionation and psychotic symptoms that characterize schizophrenia, the current review should help to focus neuroanatomic models of the illness.

This work was supported by the Human Brain Project of the National Institute of Mental Health (Grant No. R01-MH074457-01A1).

Dr. Bullmore is head of the GlaxoSmithKline Clinical Unit at Cambridge. None of the other authors reported any biomedical financial interests or potential conflicts of interest.

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