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Brain Anatomical Abnormalities in High-Risk Individuals, First-Episode, and Chronic Schizophrenia: An Activation Likelihood Estimation Meta-analysis of Illness Progression

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Objective: **The present study reviewed voxel-based morphometry (VBM) studies on high-risk individuals with schizophrenia, patients experiencing their first-episode schizophrenia (FES), and those with chronic schizophrenia. We predicted that gray matter abnormalities would show progressive changes, with most extensive abnormalities in the chronic group relative to FES and least in the high-risk group.** ***Method:*** **Forty-one VBM studies were reviewed. Eight high-risk studies, 14 FES studies, and 19 chronic studies were analyzed using anatomical likelihood estimation meta-analysis.** ***Results:*** **Less gray matter in the high-risk group relative to controls was observed in anterior cingulate regions, left amygdala, and right insula. Lower gray matter volumes in FES compared with controls were also found in the anterior cingulate and right insula but not the amygdala. Lower gray matter volumes in the chronic group were most extensive, incorporating similar regions to those found in FES and high-risk groups but extending to superior temporal gyri, thalamus, posterior cingulate, and parahippocampal gryus. Subtraction analysis revealed less frontotemporal, striatal, and cerebellar gray matter in FES than the high-risk group; the high-risk group had less gray matter in left subcallosal gyrus, left amygdala, and left inferior frontal gyrus compared with FES. Subtraction analysis confirmed lower gray matter volumes through ventral-dorsal anterior cingulate, right insula, left amygdala and thalamus in chronic schizophrenia relative to FES.** ***Conclusions:*** **Frontotemporal brain structural abnormalities are evident in nonpsychotic individuals at high risk of developing schizophrenia. The present meta-analysis indicates that these gray matter abnormalities become more extensive through first-episode and chronic illness. Thus, schizophrenia appears to be a progressive cortico-striato-thalamic loop disorder.**

Key words: meta-analysis/brain structure/high-risk group/schizophrenia

Introduction

Several recent structural brain imaging meta-analytic studies have demonstrated brain abnormalities in patients with schizophrenia at different stages of the illness.[1–5] In particular, patients with first-episode schizophrenia (FES) already have smaller whole-brain volume, with greater lateral ventricular volume.[3] Frontal[6–9] and temporolimbic[7,8] volumes have been reported to be smaller at first episode, while the basal nuclei are also affected early in the illness.[9,10] However, the extent of abnormalities observed in FES varies considerably from study to study. Similarly, in patients with chronic schizophrenia smaller mean cerebral volumes and greater total ventricular volumes, with a reduction in hippocampus and parahippocampi size bilaterally, have been reported.[5,11,12] Bilateral volume deficits in amygdala, frontal lobe, and temporal lobe appear to persist to chronic stages[12] with a recent comprehensive meta-analysis describing progression of neocortical but not limbic cortical gray matter decrease with illness.[4]

Whether structural abnormalities are found in nonpsychotic relatives of people with schizophrenia is much less clear-cut. Nonpsychotic relatives of patients may share a genetic liability to schizophrenia. Therefore, brain structure abnormalities have been predicted to extend to those nonpsychotic relatives but in a less severe form. Consistent with this, preliminary studies have shown that nonpsychotic relatives of patients with schizophrenia have regional volume reductions in frontotemporal

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regions,[13–15] although other evidence suggests that features in these groups are rather mild[16] or restricted to anterior cingulate[17] or cerebellum.[18] Considering data from patient relatives as a proxy measurement of subclinical or early disease, some authors have suggested that progressive gray matter reduction in schizophrenia is superimposed on a preexisting volume deficit.[19] The implication is that schizophrenia results from an early predisposition or developmental insult that gradually worsens.[20,21]

Given the plethora of imaging data now available at different stages of the illness, it is timely to apply a meta-analytic approach to map hypothesized progressive developmental pathology. If the hypothesis holds, nonpsychotic relatives of patients with schizophrenia, sharing a genetic liability to schizophrenia, would be predicted to have brain structural abnormalities in similar regions to patients early in their illness. These abnormalities should be exacerbated by chronicity. We therefore conducted a meta-analytical analysis of voxel-based morphometric (VBM) studies of gray matter brain abnormalities in schizophrenia and high-risk individuals. The high-risk group was defined as first- or second-degree relatives to schizophrenia patients or meeting the criteria of Personal Assessment and Crisis Evaluation (PACE).[22]

Method

Article Selection

Studies were searched in the PubMed and MEDLINE database, using the key words "voxel-based morphometry" and "schizophrenia," or "VBM" and "schizophrenia," respectively. For high-risk group, we used additional key words such as "sibling," "relative," "twin," or "high risk." Among the up to 200 result articles, we choose studies considering the following inclusion criteria: (1) they were research articles, (2) they used VBM analysis to investigate gray matter density change of magnetic resonance imaging (MRI) dataset, (3) they directly compared a group of subjects with schizophrenia or high risk with a healthy control group, and (4) the results were normalized to a stereotactic standardized space such as Montreal Neurological Institute (MNI) space or Talairach space,[23] and the coordination of the activation areas was explicitly reported. In addition, we searched the reference lists of the studies identified for inclusion.

The high-risk group was defined as first- or second-degree relatives of patients with schizophrenia, those meeting the criteria of PACE,[22] or those with a modification of the catechol-*O*-methyltransferase gene.[24] As a result, 8 studies with 601 high-risk individuals were included in the high-risk group of the activation likelihood estimation (ALE) meta-analysis.

The FES group was principally defined by the authors of any given study. Those included in the FES group of studies had a duration of illness less than 1 year. Two studies reporting results from patients with first-episode psychosis were also included.[25,26] As a result, 14 studies with 466 patients were included in the FES group of the ALE meta-analysis.

Great care was taken to make sure that the group of studies on chronic schizophrenia did not include FES patients. Therefore, although other meta-analyses may have included a broader range of "chronic" studies,[4] we excluded several for the following reasons. Some articles grouped together chronic and FES patients (eg, Hone et al[16] and Antonova et al[27]). In other studies of chronic schizophrenia, if the lower range of the duration of illness was less than 1 year or mean duration was less than 5 years, studies were excluded.[28–33] Articles that did not report the duration of illness explicitly were also excluded (eg, García-Martí et al,[34] Moorhead et al[35], and Tregellas et al[36]). Because there are so many more articles relating to chronic schizophrenia than first-episode or high-risk groups, this stricter criterion than previous[4] had the advantage of lessening the impact of publication bias toward chronic studies. There were 19 studies comprising a total of 808 strictly defined chronic patients included in the ALE meta-analysis.

Anatomical Likelihood Estimation

The ALE analyses were conducted in the Talairach space. Anatomical coordinates reported in the MNI space were converted into Talairach space using Lancaster transform.[62] Where Brett's formulation had been used to convert from MNI to Talairach,[63] results were first converted back to MNI space and then transformed into Talairach space using Lancaster's method. Where information regarding the stereotactic space used to report the results was unclear, we contacted the authors for further details.

The activation likelihood estimation meta-analysis[64] was carried out using GingerALE software.[65] Although originally applied to functional imaging studies, the method has now been widely applied to examine anatomical image datasets.[66] The idea behind ALE analysis is that peak coordinates reported in VBM studies should be viewed as probability distributions around these coordinates.[64] Practically, the ALE map was constructed based on foci reported in table 1 for each specific contrast, with a smoothing kernel of full-width at half-maximum of 10 mm. Then, activation maps with randomly distributed foci equal to the number of foci in the ALE analysis were simulated by 5000 permutations to sample the null hypothesis.

Three ALE maps were constructed. First, we examined gray matter in the high-risk group compared with controls reported in 8 articles (43 foci). Second, we examined gray matter in first-episode patients compared with healthy controls reported in 14 articles (156 foci). Third, we examined gray matter in chronic schizophrenia patients compared with healthy controls reported in 19 articles (223 foci). The clusters identified in each

Table 1. Summary of Articles Included in the Meta-analysis

Group	No.	Study	Number of Patients	Male	Age (y)	Number of Controls	Male	Duration of Illness	Medication	Scanner	Type
Chronic	1	Ananth et al[6]	20	10	37.8	20	10	15.8	All	2.0 T	Chronic
	2	Bassitt et al[37]	50	38	31.7	30	21	11.4	All	1.5 T	Chronic
	3	Cooke et al[38]	52	40	38.4	30	24	13.9	All	1.5 T	Chronic
	4	Giuliani et al[39]	41	32	39	34	17	17.3	All	1.5 T	Chronic
	5	Hirao et al[40]	20	10	36.7	20	10	10.6	All	3 T	Chronic
	6	Hulshoff Pol et al[41]	159	112	35.6	158	106	12.3	All	1.5 T	Chronic
	7	Marcelis et al[18]	31	15	30.7	27	12	8.5	28 y	1.5 T	Chronic
	8	Martí-Bonmatí et al[42]	21	21	39	10	10	15	All	1.5 T	Chronic
	9	McIntosh et al[13]	26	13	36.9	49	23	15.3	N/A	1.5 T	Chronic
	10	Meisenzahl et al[43]	72	56	35.6	177	123	9.5	86.1% y	1.5 T	Chronic
	11	Neckelmann et al[44]	12	N/A	19–51	12	N/A	8.7	y	1.5 T	Chronic
	12	Ohnishi et al[45]	47	24	44.2	76	30	19.3	All	1.5 T	Chronic
	13	Paillère-Martinot et al[46]	20	20	29	20	20	10	18 y	1.5 T	Chronic
	14	Shapleske et al[47]	72	72	34.1	32	32	11.5	All	1.5 T	Chronic
	15	Sigmundsson et al[48]	27	26	34.9	27	25	13.9	N/A	1.5 T	Chronic
	16	Wilke et al[49]	48	27	33	48	27	8.59	43 y	1.5 T	Chronic
	17	Wolf et al[50]	28	20	33.1	14	9	5.8	27 y	1.5 T	Chronic
	18	Wright et al[51]	42	31	34.6	52	34	12.2	N/A	1.0 T	Chronic
	19	Yamada et al[52]	20	10	38.8	20	10	11.6	All	3 T	Chronic
FES	20	Chua et al[10]	26	12	32	38	18	0.33	None	1.5 T	First episode
	21	Douaud et al[53]	25	18	16.3	25	17	1.4	All	1.5 T	First episode
	22	Janssen et al[26]	25	19	15.4	51	35	0.29	All	1.5 T	First episode
	23	Jayakumar et al[54]	18	9	24.9	18	9	0.86	None	1.5 T	First episode
	24	Job et al[7]	34	23	21.4	36	17	N/A	N/A	1.0 T	First episode
	25	Kaspárek et al[55]	22	22	23.7	18	18	T20-89d	None	1.5 T	First episode
	26	Kubicki et al[8]	16	14	26.7	18	16	0.14	All	1.5 T	First episode
	27	Lui et al[56]	68	38	24.2	68	37	0.72	None	3 T	First episode
	28	Meisenzahl et al[43]	93	67	28.2	177	123	0.76	84.9% y	1.5 T	First episode
	29	Prasad et al[25]	15	a11	a24.7	12	a6	2.32	None	1.5 T	First episode
	30	Salgado-Pineda et al[9]	13	13	23.8	13	13	N/A	None	1.5 T	First episode
	31	Schaufelberger et al[57]	62	44	27.6	94	53	0.48	69% y	1.5 T	First episode
	32	Whitford et al[58]	31	20	19.3	30	20	<3 m	27 y	1.5 T	First episode
	33	Yoshihara et al[59]	18	9	15.8	18	9	1.2	17 y	1.5 T	First episode
High risk	34	Borgwardt et al[14]	35	22	23.7	22	13			1.5 T	PACE criteria
	35	Honea et al[16]	213	89	36.5	212	103			1.5 T	Siblings
	36	Job et al[17]	146	74	21.2	36	17			1.0 T	First- /second-degree relatives
	37	Lui et al[60]	10	3	41.4	10	4			3 T	Parents
	38	Marcelis et al[18]	32	14	35.5	27	12			1.5 T	First-degree relatives
	39	McIntosh et al[61]	50	25	36.4	48				1.5 T	First- /second-degree relatives
	40	McIntosh et al[24]	75	57	22.0	N/A				1 T	COMT gene
	41	Meisenzahl et al[15]	40	25	25.0	75	46			1.5 T	BSABS and PACE

Note: FES, first-episodic schizophrenia; BSABS, Bonn Scale for Assessment of Prodromal Symptoms; PACE, Personal Assessment and Crisis Evaluation; COMT, catechol-*O*-methyltransferase.

meta-analysis were obtained after controlling the false discovery rate at $P < .01$ and applying a cluster extent threshold of 100 voxels.

In order to compare gray matter differences between high-risk group and FES group, subtraction meta-analyses were performed. A subtraction meta-analysis yields an ALE map that shows regions in which the 2 groups of foci are significantly different. However, because there were more studies in the FES group ($n = 14$) than in the high-risk group ($n = 8$), more coordinates were reported by FES studies than high-risk studies. The different number of studies in 2 groups could therefore bias the analysis toward finding more extensive changes in FES group. Ellison-Wright et al[4] addressed this problem by randomly selecting coordinates from the group of studies with more foci, making the number of foci the same as the number in the group

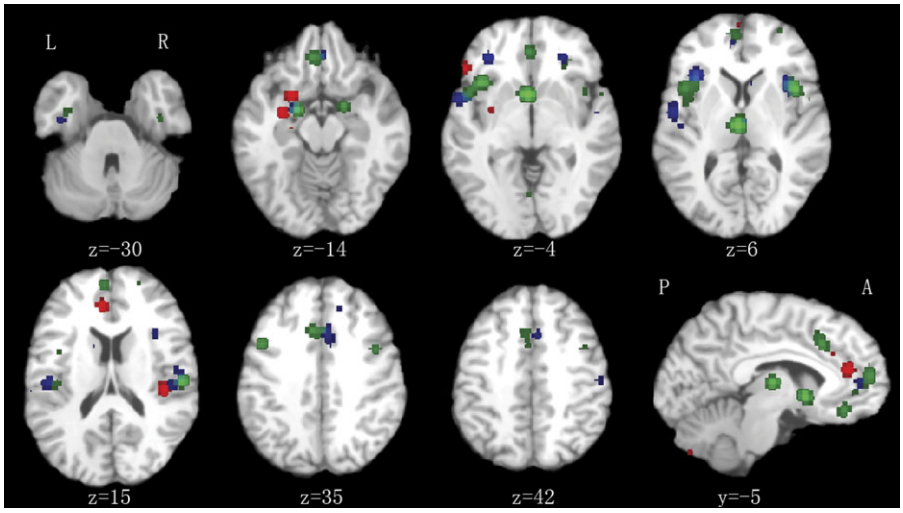

Fig. 1. Control Comparison Analyses. Gray matter volumes lower in high-risk group (red), first episodic group (blue), and chronic group (green) compared with healthy controls. Significance thresholded with a false discovery rate at $P < .01$. z represents the z coordinates in Talairach space. L, left; R, right; A, anterior; P, posterior.

reporting fewer coordinates. However, 2 factors could cause different numbers of coordinates in each group of studies. The first is a different number of studies in the 2 groups, and the second is a different mean number of foci reported in studies contained in the 2 groups. For example, in the current high-risk vs FES subtraction analysis, the mean number of foci in high-risk group was 43/8 = 5.375 and the mean number of foci in FES group was 156/14 = 11.14. This difference in mean number of foci in high-risk group and FES group potentially indicates more widespread abnormalities in FES group than high-risk group, and to retain this information in the subtraction ALE analysis we balanced the studies represented in each group by taking a proportion of data from the bigger study group as follows:

In the FES vs high-risk subtraction analysis, the proportion of coordinates "x" from FES studies compared with the high-risk data was

$$x = 156(\text{total number of foci in FES}) \times 8(\text{number of studies in high risk}) / 14(\text{number of studies in FES}) = 89.$$

Similarly, the proportion of foci "x" from the chronic group used in the chronic vs FES subtraction analysis was

$$x = 223(\text{total number of foci in chronic}) \times 14(\text{number of studies in FES}) / 19(\text{number of studies in chronic}) = 164.$$

Results

Demographic and medication informations are summarized in the table 1. The mean age of the patients in chronic group (mean 35.7 y) was much older than patients in FES group (mean 23.1 y) and high-risk group (mean 30.2 y). The individuals in the high-risk group were also older than in FES group. Most of the chronic patients received antipsychotic medication, while the patients in FES group were mixed. Six out of 14 studies of FES included patients who were antipsychotic naive, but in the remainder most of the patients received antipsychotic medication.

High-Risk Group

As illustrated in figure 1 and table 2, compared with healthy control group, there was significantly less gray matter in bilateral anterior cingulate gyrus (Brodmann area [BA] 32/24), right insula (BA 13), left amygdala, left subcallosal gyrus (BA 34), and left inferior frontal gyrus (BA 47) of high-risk individuals. Of these regions, the left amygdala, subcallosal gyrus, and inferior frontal gyrus were also smaller than in the FES group, see figure 2 and table 3.

First Episodic Schizophrenia

As illustrated in figure 1 and table 2, the FES group, compared with healthy control group, had significantly less gray matter in the anterior cingulate right insula (BA 13). However, FES gray matter volume deficits involved more of the left lateral prefrontal lobe (BAs 10, 44) in addition to right BA 8, bilateral postcentral gyrus (BA 1/2/40), left temporal lobe (BAs 41, 42, 34), left insula (BA 13), right cerebellum, and right caudate nucleus. The result was similar when FES was compared with the high-risk group, see figure 2 and table 3.

Chronic Schizophrenia

Patients with chronic schizophrenia had lower gray matter volumes in the anterior cingulate and right insula

Table 2. ALE Results of Gray Matter Reduction in High-risk, FES, and Chronic Individuals

Volume (mm^3)	Peak ALE Value	Peak coordinates			Label
		x	*y*	*z*	
High-risk group					
824	0.010949	42	−28	16	R insula (BA 13)
800	0.011203	−28	−8	−12	L amygdala
560	0.011405	−6	36	16	L anterior cingulate (BA 32)
560	0.007998	4	30	20	R anterior cingulate (BA 24)
	0.007454	6	30	26	R anterior cingulate (BA 32)
536	0.012022	−22	6	−14	L subcallosal gyrus (BA 34)
432	0.010776	−48	26	−2	L inferior frontal gyrus (BA 47)
FES group					
2616	0.018719	−46	−20	12	L transverse temporal gyrus (BA 41)
	0.016219	−52	−8	6	L superior temporal gyrus (BA 22)
	0.015184	−58	−28	12	L superior temporal gyrus (BA 42)
1576	0.015055	50	−10	12	R precentral gyrus (BA 13)
	0.013404	48	−24	18	R insula (BA 13)
1392	0.024821	34	16	10	R insula (BA 13)
1000	0.0236	−34	20	6	L insula (BA 13)
1000	0.015507	6	16	38	R cingulate gyrus (BA 32)
	0.011044	8	26	32	R cingulate gyrus (BA 32)
976	0.015917	−54	2	−4	L superior temporal gyrus (BA 22)
	0.010599	−40	6	0	L insula
768	0.014903	−20	−4	−18	L amygdala
528	0.01845	24	34	−8	R inferior frontal gyrus (BA 47)
504	0.017395	52	−8	−8	R superior temporal gyrus (BA 22)
456	0.017448	−32	34	−6	L middle frontal gyrus (BA 47)
416	0.014218	−48	6	22	L inferior frontal gyrus (BA 44)
288	0.012031	−8	46	8	L medial frontal gyrus (BA 10)
224	0.011605	10	10	12	R caudate
216	0.011588	52	−20	44	R postcentral gyrus (BA 2)
200	0.011739	−60	−18	20	L postcentral gyrus (BA 40)
192	0.012533	2	36	−16	R medial frontal gyrus (BA 11)
184	0.011727	28	−44	−34	R cerebellum
176	0.012417	−38	−14	−30	L uncus (BA 20)
Chronic schizophrenia group					
4832	0.022295	−36	16	−4	L inferior frontal gyrus (BA 47)
	0.021812	−46	8	0	L insula (BA 13)
	0.012372	−40	0	8	L insula (BA 13)
	0.012334	−38	0	14	L insula (BA 13)
2976	0.019676	−4	52	12	L medial frontal gyrus (BA 10)
	0.018219	−6	34	−14	L medial frontal gyrus (BA 11)
	0.017656	0	38	−4	L anterior cingulate (BA 32)
2336	0.029234	40	10	4	R insula (BA 13)
	0.014545	54	4	0	R superior temporal gyrus
1832	0.031679	−2	6	−2	L anterior cingulate (BA 25)
1744	0.018575	−6	18	34	L cingulate gyrus (BA 32)
	0.018075	2	18	32	R cingulate gyrus (BA 32)
	0.012224	−2	8	40	L cingulate gyrus (BA 32)
1648	0.028163	−2	−18	6	L thalamus
1208	0.019934	−44	8	36	L middle frontal gyrus (BA 9)
	0.017604	−50	6	30	L inferior frontal gyrus (BA 9)
840	0.024792	−16	−6	−12	L amygdala
792	0.023959	56	−20	18	R postcentral gyrus (BA 40)
584	0.019595	18	−4	−12	R amygdala
416	0.014732	30	54	10	R superior frontal gyrus (BA 10)
392	0.017153	42	4	38	R middle frontal gyrus (BA 6)
328	0.013756	−40	−22	14	L insula (BA 13)
160	0.013739	−32	−8	−32	L uncus (BA 20)
160	0.013219	12	−36	0	R parahippocampal gyrus (BA 27)
136	0.011935	26	28	−2	R inferior frontal gyrus (BA 47)

Note: Abbreviations are explained in the first footnote to table 1. ALE, activation likelihood estimation; R, right; L, left; BA, Brodmann area.

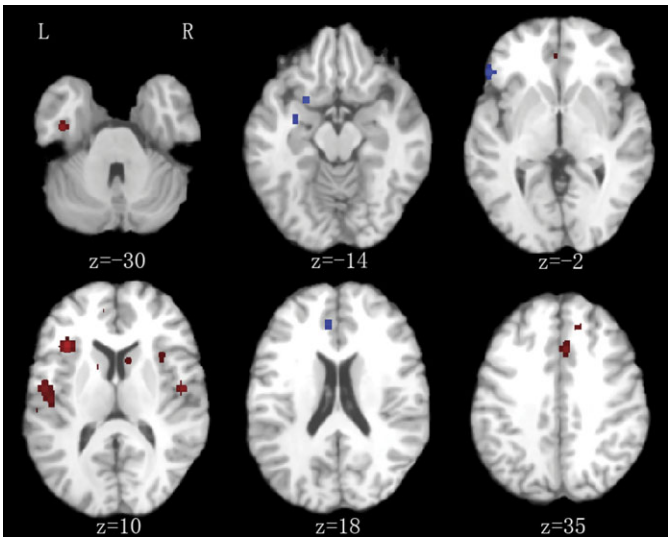

Fig. 2. Subtraction Analysis in First-Episode Schizophrenia (FES) Vs High-Risk Group. Red: lower gray matter volume in FES group. Blue: lower gray matter volume in high-risk group. Significance thresholded with a false discovery rate at $P < .01$. z represents the z coordinate in the Talairach space. L., left; R., right.

compared with controls and FES. In addition, patients with chronic schizophrenia had less gray matter in the temporal lobe (bilateral BA 22, right parahippocampus, left amygdala), left frontal lobe (BAs 9, 11, 8, 32), left insula, thalamus, and left posterior cingulate gyrus compared with controls. Volumes of many of these regions were also lower in chronic disease than FES (figure 3 and table 4). However, the volume of the right postcentral gyrus (BA 2) was lower in FES than chronic schizophrenia.

Discussion

The high-risk group had lower anterior cingulate and right insula volumes than controls. Gray matter in these same regions was also lower in FES and the chronic condition relative to controls. The FES group had lower gray matter volumes in frontal, temporal, striatal, and cerebellar regions compared with both controls and high-risk groups. The chronic group had lower gray matter volumes in similar frontotemporal regions compared with controls and FES groups. However, gray matter volumes in left dorsolateral prefrontal lobe and the thalamus were also lower compared with FES and controls.

Previous meta-analyses of brain volume changes in schizophrenia have generally considered "region-of-interest" (ROI)–based MRI studies.[1–3,5] However, ROI studies are challenging because they tend to rely on manual tracing methods. The region to be quantified therefore must have identifiable boundaries and be large enough to visualize and trace. Thus, measurement is restricted to relatively coarse or lobar targets, and more subtle anatomical differences cannot be easily resolved. Moreover, targets for quantification in ROI are necessarily limited to measurement of a priori determined regions, and unpredicted differences will be missed. Automated "voxel-based" studies, which quantify every "volume element" in whole brain, overcome these limitations to some degree. However, until techniques such as ALE became available, it has not been possible to integrate data from voxel-based studies of schizophrenia into meta-analyses. Nevertheless, there are broad similarities between the results reported here and those found by more conventional means. In particular, Shenton et al[5]

Table 3. Subtraction ALE Results of Gray Matter Reduction in High-Risk and FES Individuals

Volume (mm^3)	Peak ALE Value	Peak Coordinates			Label
		x	*y*	*z*	
Greater GM reduction in high-risk group compared with FES					
224	−0.01077	−50	26	−2	L inferior frontal gyrus (BA 47)
184	−0.01151	−22	6	−14	L subcallosal gyrus (BA 34)
128	−0.00977	−30	−8	−12	L amygdala
128	−0.00988	−6	36	18	L anterior cingulate (BA 32)
Less GM reduction in high-risk group compared with FES					
1728	0.016143	−52	−8	6	L superior temporal gyrus (BA 22)
	0.011673	−46	−20	12	L transverse temporal gyrus (BA 41)
1184	0.023268	−34	20	6	L insula (BA 13)
448	0.012066	6	18	38	R cingulate gyrus (BA 32)
400	0.013157	48	−10	12	R precentral gyrus (BA 13)
368	0.012289	−18	−2	−22	L uncus (BA 34)
320	0.011672	28	−44	−34	R cerebellum
272	0.01241	−38	−14	−30	L uncus (BA 20)
224	0.010423	10	8	14	R caudate
192	0.009565	−2	−14	4	L thalamus
192	0.009968	−12	6	12	L caudate

Note: Abbreviations are explained in the first footnote to table 1.

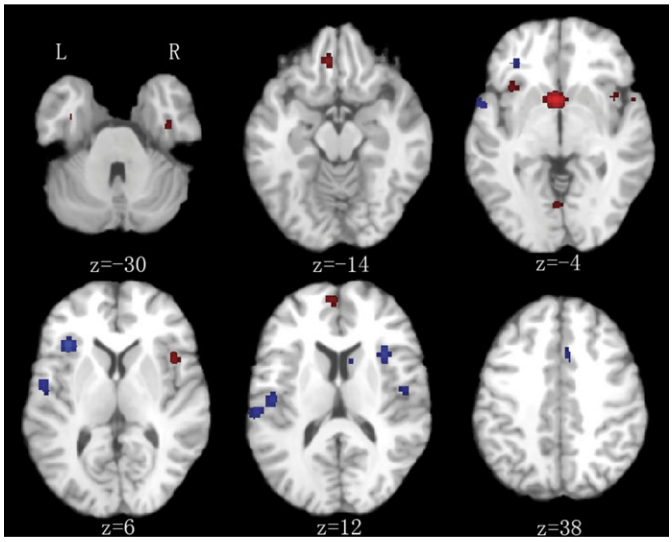

Fig. 3. Subtraction Analysis Chronic Vs First-Episode Schizophrenia (FES) Group. Red: lower gray matter volume in chronic schizophrenia. Blue: lower gray matter volume in FES. Significance thresholded with a false discovery rate at $P < .01$. z represents the *z* coordinate in the Talairach space. L, left; R, right.

reviewed 193 studies of schizophrenia and concluded that there was moderate to strong evidence for frontal lobe, medial temporal lobe, basal ganglia, and thalamic abnormalities that fits the patterns described here.[5] Moreover, a "progression of pathology with illness chronicity similar to that presented here has been suggested by ROI meta-analyses." For example, Vita et al[2] also found that the amygdala is unaffected in FES, while Wright et al[12] found amygdala deficits in more chronic patients, again similar to our findings.

Interestingly, the seminal ALE study of FES and chronic schizophrenia conducted by Ellison-Wright et al[4] did not find evidence to support extension of pathology to the amygdala with chronic illness. Otherwise, our studies generated fairly consistent results concerning FES and chronic patients. Both studies found caudate deficits in FES that were absent later in the disease and more extensive frontal (especially anterior cingulate) and insula deficits in chronic illness. In the present study, we defined "chronic" illness quite strictly. Thus, we excluded chronic studies if they included patients whose duration of illness was less than 1 year or if the mean duration was less than 5 years.[28–33] We also excluded studies that did not state duration of illness (eg, García-Martí et al,[34] Moorhead et al,[35] and Tregellas et al[36]). This meant that the number of studies of chronic schizophrenia was fewer than in Ellison-Wright's.[4] The more constrained analysis aimed to minimize potential overlap between FES and chronic patient samples and may have contributed to the differences between our 2 studies.[4]

The present results also suggest a link between predisposition to schizophrenia and structural anomalies of the anterior cingulate and right insula. Compared with

Table 4. Subtraction ALE Results of Gray Matter Reduction in FES and Chronic Individuals

Volume (mm^3)	Peak ALE Value	Peak Coordinates			Label
		x	*y*	*z*	
Greater GM reduction in FES compared with chronic group					
944	−0.01541	−52	−8	6	L superior temporal gyrus (BA 22)
	−0.01546	−46	−18	10	L transverse temporal gyrus (BA 41)
664	−0.0225	−34	20	6	L insula (BA 13)
512	−0.0171	34	16	12	R insula (BA 13)
448	−0.01491	−58	−28	12	L superior temporal gyrus (BA 42)
408	−0.01723	52	−8	−8	R superior temporal gyrus (BA 22)
320	−0.01427	−56	2	−4	L superior temporal gyrus (BA 22)
208	−0.01331	−48	6	22	L inferior frontal gyrus (BA 44)
168	−0.01463	24	34	−8	R inferior frontal gyrus (BA 47)
136	−0.01261	−32	32	−4	L inferior frontal gyrus (BA 47)
120	−0.01217	50	−12	12	R precentral gyrus (BA 13)
120	−0.01197	6	14	38	R cingulate gyrus (BA 32)
Greater GM reduction in chronic compared with FES group					
1896	0.031174	−2	6	−2	L anterior cingulate (BA 25)
984	0.022839	42	10	2	R insula (BA 13)
544	0.015637	−4	52	14	L medial frontal gyrus (BA 9)
392	0.015613	−6	34	−14	L medial frontal gyrus (BA 11)
272	0.013896	−34	16	−6	L inferior frontal gyrus (BA 47)
168	0.012403	−2	−70	−4	L cerebellum
160	0.015129	56	−22	16	R postcentral gyrus (BA 40)
144	0.012727	38	−12	−30	R uncus (BA 20)

Note: Abbreviations are explained in the first footnote to table 1.

control groups, there was less gray matter in the vicinity of these regions at each stage of illness. Because control group contrasts were entirely separate analyses involving multiple different samples, the coordinates generated were unlikely to fully overlap. That is, from the control group contrasts we cannot say for sure if the pattern is truly progressive. Results from the subtraction analysis help address this issue. The FES/high-risk subtraction analysis indicated that gray matter volumes in the dorsal anterior cingulate gryus became lower from high risk to acute illness (figure 2, level $z = 36$) and right insula (figure 2, level $z = 0$). The chronic/FES subtraction analysis showed even more extensive gray matter change throughout the ventral-dorsal anterior cingulate (figure 3, $z = 4$ through 28) and right insular cortex (figure 3, $z = -4$ through 4) with chronicity. This subtraction analysis also indicated that gray matter deficits in chronic condition became extensive in the left amygdala and thalamus compared with FES.

The anterior cingulate is a critical node integrating the emotion and executive function performance of the limbic and frontal lobe, respectively.[67,68] As such, it is central to cognition[69] and is needed for response selection,[70–72] error detection,[73,74] and monitoring of reward contingencies.[75] Adolescents with schizotypal personality disorder (considered at high risk for developing schizophrenia) who have ''negative'' symptoms also have executive dysfunction.[76] Smaller volumes of the anterior cingulate are associated with greater executive function difficulty[77] and with more severe Schneiderian first-rank symptoms.[78] Thus, there appears to be a convergence of evidence for a link between smaller anterior cingulate volumes, cognitive difficulties, and the schizophrenia phenotype.

The results from this meta-analysis contradict other findings of larger anterior cingulate volumes in schizophrenia.[79] Interestingly, that study showed that the greatest cingulate cortical thickness correlated with the duration of exposure to typical antipsychotic medication and was unrelated to chronicity. This raises the important issue of the impact drug treatment may have on brain morphology. Antipsychotic medications may act to increase regional brain volumes, especially in the caudate nucleus and anterior cingulate.[80–83] Such antipsychotic-induced hypertrophy[82] may perhaps contribute to these divergent findings, but the present meta-analysis suggests that, in general, anterior cingulate volumes are lower in people predisposed to and suffering from schizophrenia.

The basal ganglia appear to be especially sensitive to medication. Prior to exposure to antipsychotic medication, patients with schizophrenia have smaller caudate nuclei, putamen, and nucleus accumbens.[9,10,82–85] Following treatment, subcortical enlargement occurs,[80–83,86] although the effect may be more pronounced with typical rather than atypical drug options.[82] This reversal of caudate volume deficits with exposure to medication may explain why caudate deficits were not found in the chronic samples. That lower caudate size was only noted in FES and not the high-risk group in our study agrees with a recent proposal that small caudate volumes may serve as a useful biological marker for onset of psychosis the size of which is thereafter modified by antipsychotic drug treatment.[10,80]

Our finding that both predisposition to schizophrenia and progression of schizophrenia is associated with lower right insula volumes is important. The insula may act as a relay or interface between the frontal and temporal lobes, and its involvement in schizophrenia has been suggested to be an ''extension'' of primary frontal and temporal lobe pathology in schizophrenia.[87] Decreased activation of the insula during the classic frontal lobe task (verbal fluency) in schizophrenia is consistent with this hypothesis.[88] The insula has been reported to activate during instances of response inhibition failure,[89,90] and this role in behavior suppression is in conjunction with the anterior cingulate.[90,91] The insula also has a well-recognized role in emotion processing, especially in assigning emotional meaning to bodily feelings or emotion simulation.[92,93] Patients with schizophrenia have difficulty with socioemotional simulation or mental representation of emotions,[94] and increased insular activation has been linked to somatic hallucinations in schizophrenia.[95] Thus, our finding of a preexisting insular anomaly in high-risk samples may explain accumulating evidence for emotional difficulties in high-risk individuals that are similar to, if milder than, full-blown clinical disease.[96]

We suggest that the present meta-analysis is consistent with the conceptualization of schizophrenia as a progressive disorder.[20,21] The results here confirm structural brain abnormalities in those at high risk of the disorder, which are likely to be genetically determined. Brain abnormalities at first presentation include similar regions, but additional fronto-striatal-temporal pathology emerges. Finally, by chronic illness, the gray matter volume lowering has progressed further not only within the same regions but also involving more prefrontal cortical and thalamic loci. This cortico-thalamic pathology maps convincingly to the neurochemical circuitry systems implicated in schizophrenia, namely, cortico-thalamic loop systems, regulated through a complex interplay of glutmate, γ-aminobutyric acid, and dopamine neurotransmission.[97]

Abnormalities in glutamate receptors are thought to contribute especially to the cognitive difficulties and negative symptoms of schizophrenia.[98] Because glutamate receptor signaling is a critical regulator of neuronal development and cell death, abnormalities in glutamate transmission could therefore partly explain the neurodevelopmental origins, progressive loss of gray matter, and cognitive impairment found in schizophrenia. In their revised excitotoxic hypothesis of schizophrenia, Deutsch et al[99] predicted that progressive cell loss in cortical areas occurs via disinhibition of glutamate projections. They

suggested that support for this hypothesis would come from ''anatomic evidence'' of progression along with the increasing cognitive impairment and negative symptomatology in chronic illness.[99] In the absence of substantial long-term follow-up studies, the present meta-analysis fits with their prediction and offers a series of targets to further investigate neurochemical perturbation in schizophrenia. A more recent evaluation of neurochemistry in schizophrenia also highlighted the potential for glutamate excitotoxicity in schizophrenia.[100] Thus, further investigation of a hypothethical link between excitotoxic levels of cortical glutamate and macroscopic gray matter differences in brain regions identified here may provide new leads and options for treatment.

We acknowledge that our study is not without limitations. While we have interpreted our findings as reflecting ''progression,'' we use this term quite loosely. To truly observe progression, longitudinal studies are needed. Moreover, we acknowledge that, given the high-risk individuals included in our analysis were older than the first-episode group, these ''high-risk'' patients would be unlikely to develop schizophrenia. At most, we can interpret the contribution of findings from this group of studies as pertinent to shared genetic factors. The patients in first-episode and chronic studies would presumably have these shared genetic factors in addition to other disease-specific genetic or environmental factors. Although the large majority of the first-episode studies did investigate only patients with schizophrenia, and excluded other psychosis, some did not. Prasad et al[25] included patients with schizoaffective disorder, and Janssen et al[26] included patients with affective psychosis and other psychoses. In the latter study, the authors followed up their cohort and found common gray matter deficits in schizophrenia and bipolar patients that they interpreted as consistent with a shared pathology. Thus, it is possible that patients without a strict diagnosis of schizophrenia may have contributed partly to the results we reported, but given they were a relatively small proportion of the total patient number, we expect that the influence was minimal. An additional concern is that the mean age of individuals in the chronic studies was much older than the other groups making age and important confounder. At present, the ALE method does not accommodate covariables in the analysis. Lastly, the individual studies incorporated are of different sample sizes and use variable statistical thresholds for reporting results that are not accounted for in the meta-analysis reported here. Our hope is that future versions of the software will help us address these outstanding issues.

The quantitative meta-analytic method adopted allows a fast synthesis of large amounts of detailed neuroimaging data; the method is subject to the general limitation common to all meta-analysis, namely, that studies with negative findings are less likely to be published and therefore cannot influence the meta-analysis results. Related to this is the problem that many fewer articles comparing high-risk groups with controls have been published compared with studies of people with full-blown illness. This means that fewer foci can be included from high-risk groups. The ALE method is known to be sensitive to the number of included foci, but the optimal number for analyses has not yet been determined.[65] However, a sizeable number of foci from high-risk control comparison studies[45] were included in the present analysis, and the substraction analysis attempted to balance the foci contained in the analysis to counter this bias.

In conclusion, mapping the progressive changes in schizophrenia, from shared genetic factors through to chronic illness, goes some way toward clarifying potential markers for disease risk (anterior cingulate and right insula volume reduction), disease onset (caudate volume reduction), and progression to chronic stages (thalamic involvement). We therefore hope that this approach can open new avenues for research by highlighting targets for treatment both early and late in the illness.

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