ARCHIVAL REPORT

Progressive Reduction in Cortical Thickness as Psychosis Develops: A Multisite Longitudinal Neuroimaging Study of Youth at Elevated Clinical Risk

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Background: Individuals at clinical high risk (CHR) who progress to fully psychotic symptoms have been observed to show a steeper rate of cortical gray matter reduction compared with individuals without symptomatic progression and with healthy control subjects. Whether such changes reflect processes associated with the pathophysiology of schizophrenia or exposure to antipsychotic drugs is unknown.

Methods: In this multisite study, 274 CHR cases, including 35 individuals who converted to psychosis, and 135 healthy comparison subjects were scanned with magnetic resonance imaging at baseline, 12-month follow-up, or the point of conversion for the subjects who developed fully psychotic symptoms.

Results: In a traveling subjects substudy, excellent reliability was observed for measures of cortical thickness and subcortical volumes. Controlling for multiple comparisons throughout the brain, CHR subjects who converted to psychosis showed a steeper rate of gray matter loss in the right superior frontal, middle frontal, and medial orbitofrontal cortical regions as well as a greater rate of expansion of the third ventricle compared with CHR subjects who did not convert to psychosis and healthy control subjects. Differential tissue loss was present in subjects who had not received antipsychotic medications during the interscan interval and was predicted by baseline levels of an aggregate measure of proinflammatory cytokines in plasma.

Conclusions: These findings demonstrate that the brain changes are not explained by exposure to antipsychotic drugs but likely play a role in psychosis pathophysiology. Given that the cortical changes were more pronounced in subjects with briefer durations of prodromal symptoms, contributing factors may predominantly play a role in acute-onset forms of psychosis.

Key Words: Inflammation, MRI, prefrontal cortex, prodromal, psychosis, schizophrenia

Evidence of progressive loss of gray matter in individuals at clinical high risk (CHR) who convert to psychosis (1–7) suggests that disturbances in neuromaturational processes during the transition from adolescence to early adulthood (8–12) may play a role in onset of psychosis. However, numerous questions remain to be answered before such an interpretation would be warranted. First, this effect may be a secondary phenomenon. Antipsychotic drugs are associated with gray matter decline in animal models (13) and in patients with schizophrenia (14,15), including patients with a first episode (16). Because follow-up (FU) scans for converting CHR cases in all longitudinal magnetic resonance imaging (MRI) studies were performed after conversion, most of the converters (and relatively fewer of the nonconverters) received antipsychotic drug treatment during the interscan interval. In the only prior study to examine this question, converters who had not received antipsychotics during the interscan interval ($n = 5$) did not differ in rate of tissue loss from converters who did receive antipsychotics before the FU scan ($n = 5$) (5). However, this comparison was almost certainly underpowered to detect a difference if one exists; a more conclusive result would emerge from comparing

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Received Mar 6, 2014; revised May 17, 2014; accepted May 25, 2014.

0006-3223/$36.00
http://dx.doi.org/10.1016/j.biopsych.2014.05.023

the rate of loss among converters not exposed to antipsychotics during the interscan interval with nonconverters and control subjects.

If the accelerated gray matter loss associated with psychosis onset is not a secondary phenomenon, it could be due to factors related to the pathophysiology of schizophrenia and related disorders, such as neuroinflammation (17). Neuroinflammatory markers are elevated in postmortem neural tissue from patients with schizophrenia (18), and these same markers are associated with microglial-mediated synaptic pruning and dendritic retraction in animal models (19), providing a potential mechanistic basis for the reduced neuropil seen in patients (10). Although neuroinflammatory processes initiated during prenatal stress exposures could play a role (21), activation of such processes in association with the synaptic pruning characteristic of adolescent brain development represents an influence more proximal to psychosis onset (10,12,17,20). Recently, an elevation in plasma-based markers of inflammation and oxidative stress was found to precede and predict onset of psychosis among CHR cases (21). It remains to be determined whether such markers also predict the acceleration in gray matter loss around the time of psychosis onset.

Given that CHR cases are ascertained at different ages and at various points along the putative trajectory toward overt illness, such variability could obscure different subgroups of future converters with different profiles of change in brain structure over time. In particular, accelerated gray matter decline would be expected especially among cases with shorter durations from onset of prodromal symptoms to conversion (because the underlying pathology among cases with longer durations would likely be relatively more slowly progressing). In addition, although studies of patients with early psychosis are generally consistent in showing lower volumes in dorsolateral prefrontal, superior temporal, and parahippocampal cortex (22,23), prior longitudinal MRI studies are conflicting as to whether the steeper rate of loss in CHR converters is general or specific to these regions (1–7). However, these discrepancies may merely reflect regional differences in measurement reliability or between-study differences in statistical power.

In this multisite study, 274 CHR cases, including 35 individuals who converted to psychosis, and 135 demographically comparable healthy comparison subjects underwent MRI at baseline (BL) and at 12-month FU or the point of conversion for individuals who developed fully psychotic symptoms (24). We hypothesized that converters would show steeper rates of gray matter reduction in prefrontal, superior temporal, and parahippocampal regions compared with nonconverters and control subjects and that these effects would be present in cases without exposure to antipsychotic medications during the interscan interval. We further hypothesized that the cortical changes would be greatest among cases with a more recent onset of prodromal symptoms and that BL levels of proinflammatory cytokines would predict the rate of gray matter loss especially among converters. We also evaluated statistical power to detect differential change across brain regions by incorporating information on reliability from a traveling subjects substudy.

Methods and Materials

Subjects

The study protocol and consent form were reviewed and approved by the institutional review boards at each of the eight data collection sites (University of California, Los Angeles, Emory, Beth Israel Deaconess Medical Center, Zucker Hillside Hospital, University of North Carolina, University of California, San Diego, University of Calgary, and Yale University). Participants were evaluated using the Structured Interview for Prodromal Syndromes (25) and the Structured Clinical Interview for Axis I (DSM-IV) (26) at each assessment by trained interviewers who met high reliability standards (intraclass correlations [ICCs] = .92–.96) (24). The CHR cases met Structured Interview for Prodromal Syndromes/Scale of Prodromal Symptoms criteria for a psychosis risk syndrome (25), excluding individuals who had ever met DSM-IV criteria for a psychotic disorder. Control participants were excluded if they met criteria for a psychotic disorder, had a first-degree relative with a current or past psychotic disorder, or met prodromal criteria. General exclusions included substance dependence, neurologic disorder, or full scale IQ <70.

Subjects included in this report are those with MRI scans at BL and at 12-month FU or at the point of conversion to psychosis. Given that nearly all (37 of 41) of the converters with both BL and FU scans available had converted before the scheduled 12-month FU, few converting subjects had FU scans before conversion. To avoid mixing cases whose FU scans occurred before and after conversion, the four converters whose FU scans were obtained before conversion were excluded from the primary analyses (but included in secondary analysis). In total, 35 CHR cases who converted to psychosis, 239 CHR cases who did not convert, and 135 healthy comparison subjects had usable data and were included. These subjects were drawn from the larger pools of subjects ($n = 62$ converters, $n = 491$ nonconverters, and $n = 224$ control subjects) who had BL scans. Subjects with both BL and FU scans available did not differ from subjects with BL scans only in age, sex, education, parental education, or socioeconomic class overall or in any group separately (all p values $> .30$).[1] Demographic characteristics of the three groups are shown in Table 1. There were no significant differences in age, sex, site of origin, or socioeconomic class by group. Nonconverters had lower parental education than converters and control subjects, who did not differ. Converters and nonconverters had a higher rate of substance use disorders than the control subjects but did not differ from each other. The interscan interval was significantly briefer among converters compared with nonconverters and control subjects, who did not differ. Dividing at the median duration from onset of prodromal symptoms to FU scan among converters (26 months; range, 2–149 months) produced subgroups of 18 cases with short durations and 17 with long durations. For nonconverters, applying the same cutoff resulted in 140 cases with short durations and 76 with long durations (information on age at onset of symptoms was unavailable for the remaining 23 nonconverters).

Because this was a naturalistic study, subjects were treated in their respective communities according to prevailing standards and the judgment of the treating clinicians, who were often primary care physicians rather than psychiatrists. We collected and coded information on medication prescriptions at BL and 6-month and 12-month FU (and at the conversion assessment when relevant). Based on this information, 13 (37%) of the 35 converters and 166 (70%) nonconverters had not received antipsychotics during the interscan interval.

[1]Subjects who were not scanned had a slightly lower level of education (11.1 years vs. 11.9 years) and included a greater proportion of females (49% vs. 42%) compared with subjects who were scanned but did not differ on other demographic characteristics.

Table 1. Demographic Characteristics and Mean Rates of Change in Subcortical Regions by Group

Characteristic	Converters[a] ($n = 35$)	Nonconverters ($n = 239$)	Controls[b] ($n = 135$)	Statistic
Gender				
Male	25 (71%)	146 (61%)	73 (54%)	$\chi^2 = 3.9$, $p = .13$
Female	10 (29%)	93 (39%)	62 (46%)	
Race				
Caucasian	19 (54%)	134 (56%)	73 (54%)	$\chi^2 = .1$, $p = .92$
Non-Caucasian	16 (46%)	105 (44%)	62 (46%)	
Ethnicity				
Latino	6 (17%)	47 (20%)	20 (15%)	$\chi^2 = 1.4$, $p = .49$
Non-Latino	29 (83%)	192 (80%)	115 (85%)	
Substance Abuse Diagnosis	5 (14%)	24 (10%)	4 (3%)	$\chi^2 = 7.8$, $p = .02$
Antipsychotics[c]	22 (63%)	73 (30%)	0 (0%)	$\chi^2 = 78.8$, $p < .0001$
Age at BL	18.8 (3.8)	19.7 (4.2)	20.5 (4.6)	$F = 2.7$, $p = .06$
Parental Education	6.7 (1.4)	6.2 (1.4)	6.8 (1.4)	$F = 7.7$, $p = .0005$
Income	4.7 (1.9)	4.7 (1.9)	4.6 (1.8)	$F = .1$, $p = .89$
Interscan Interval	.9 (.5)	1.0 (.3)	1.1 (.4)	$F = 7.1$, $p = .001$
Positive Symptoms BL[d]	13.5 (3.1)	11.9 (4.1)	1.1 (1.7)	$F = 479.6$, $p < .0001$
Positive Symptoms FU[d]	18.3 (4.4)	7.8 (4.6)	.7 (1.4)	$F = 329.7$, $p < .0001$
Antipsychotic Dosage[e]	93.3 (133.7)	97.5 (122.3)	NA	
Change in Brain Volumes[f]				FDR-corrected p
Left thalamus	−.005 (.06)	.010 (.06)	.010 (.04)	.30
Right thalamus	.011 (.09)	.004 (.04)	.005 (.04)	.69
Left caudate	.015 (.05)	−.003 (.04)	−.004 (.03)	.20
Right caudate	.010 (.05)	−.004 (.04)	−.004 (.03)	.21
Left putamen	.014 (.04)	−.001 (.04)	−.001 (.04)	.20
Right putamen	.006 (.10)	.005 (.05)	.001 (.03)	.69
Left pallidum	.051 (.19)	.001 (.12)	.006 (.11)	.20
Right pallidum	.017 (.10)	.003 (.06)	−.006 (.09)	.30
Left hippocampus	−.013 (.06)	.003 (.04)	−.001 (.04)	.62
Right hippocampus	−.009 (.04)	.001 (.03)	−.002 (.03)	.30
Left amygdala	.022 (.15)	.016 (.08)	−.009 (.07)	.20
Right amygdala	.036 (.13)	.016 (.09)	−.001 (.08)	.26
Left accumbens	−.032 (.15)	−.019 (.10)	−.008 (.09)	.63
Right accumbens	−.028 (.16)	−.009 (.09)	−.023 (.07)	.36
Left lateral ventricle	.064 (.13)	.024 (.17)	.011 (.07)	.31
Right lateral ventricle	.064 (.15)	.024 (.16)	.011 (.07)	.33
Brainstem	.007 (.04)	.009 (.03)	.009 (.02)	.69
Third ventricle	.086 (.12)	.015 (.10)	.011 (.07)	.01
Fourth ventricle	.061 (.14)	.006 (.12)	.002 (.06)	.13

Values are no. (%) or mean (SD).

BL, baseline; FDR, false-discovery rate; FU, follow-up; NA, not available.

[a]A Structured Interview for Prodromal Syndromes diagnosis of a psychotic syndrome refers to psychotic symptoms of particular intensity (e.g., delusional conviction) and frequency or duration (≥1 hour/day for ≥4 days/week during the past month) or of particular impact (seriously disorganizing or dangerous), designed to operationalize the threshold for a DSM-IV psychotic disorder diagnosis. DSM-IV diagnoses of converters were as follows: schizophrenia ($n = 9$); schizophreniform disorder ($n = 9$); schizoaffective disorder, depressed type ($n = 2$); bipolar disorder with psychotic features ($n = 3$); psychosis not otherwise specified ($n = 12$).

[b]The only diagnostic exclusions for control subjects were psychotic disorders. Of control subjects, 17 (13%) had one or more DSM-IV diagnoses (8 with depression, 5 with anxiety disorders, 4 with substance use disorders, 2 with attention-deficit disorder, 1 with somatization disorder, and 1 with oppositional-defiant disorder).

[c]In addition to (second-generation) antipsychotics, 10 (29%) of the converters and 104 (44%) of the nonconverters received antidepressant medications during the interscan interval. Prescriptions for other types of medicine (stimulants, anticonvulsants, benzodiazapines) occurred infrequently (four or fewer converters).

[d]Positive symptoms reflect sum of the P1–P5 ratings on the Scale for the Assessment of Prodromal Symptoms.

[e]In chlorpromazine equivalent units (64).

[f]Mean (SD) annualized rates of change (negative values indicate shrinkage, positive values indicate expansion), with FDR corrected p values. Multiplying the values by 100 provides an index of annualized percentage change.

MRI Scans

Five sites used Siemens scanners (Siemens, Munich, Germany) and three sites used GE scanners (General Electric, Fairfield, Connecticut), all at 3 tesla. All Siemens sites used a 12-channel head coil, and all GE sites used an 8-channel head coil. Sequence parameters were optimized for each scanner manufacturer, software version, and coil configuration according to the Alzheimer's Disease Neuroimaging Initiative protocol (http://adni.loni.ucla.edu/research/protocols/mri-protocols/). Scans were acquired in the sagittal plane with a 1 mm × 1 mm in-plane resolution and 1.2-mm slice thickness. Siemens scanners used a magnetization prepared rapid acquisition gradient-echo sequence with a 256

mm (axial) × 240 mm (sagittal) × 176 mm (coronal) field of view, repetition time/echo time/inversion time = 2300/2.91/900 msec, and a 9-degree flip angle. GE scanners used an inversion recovery spoiled gradient recoil sequence with a 26-cm field of view, repetition time/echo time/inversion time = 7.0/minimum full/400 msec, and an 8-degree flip angle.

Image Processing, Quality Assurance, and Reliability

All MRI images were processed using FreeSurfer version 5.2 (http://surfer.nmr.mgh.harvard.edu/) at Yale University by investigators who had participated in the FreeSurfer training course. Surface-based cortical reconstruction was performed to extract thickness measures by calculating the shortest distance from each point on the gray/white boundary to the pial surface at each vertex, along with subcortical volumetric segmentation (27–31). The subcortical segmentation procedure assigns a neuroanatomic label to each voxel of the MRI volume using a probabilistic atlas and a Bayesian classification rule (29). The reconstructed BL and FU scans were further processed using FreeSurfer's longitudinal stream to extract change in thickness and volume estimates (32). This processing stream initializes each time point scan by using an unbiased within-subject template space and average image (33), created by robust, inverse consistent registration (34), which has been shown to increase statistical power significantly for detecting subtle changes over time (32). Supplement 1 provides details of the quality assurance procedures.

Each of the eight sites also recruited one healthy subject (four male, four female) who was scanned twice on successive days at every site to permit evaluation of between-site and test-retest reliabilities using ICCs. In addition, the Alzheimer's Disease Neuroimaging Initiative structural phantom was scanned at each site and processed using the AQUAL2 algorithm (35). We have previously reported on phantom-based performance metrics and two processing streams applied to the traveling human data: cortical pattern matching and voxel-based morphometry (36). Briefly, the eight scanners performed within the range of accepted tolerance according to the phantom-based metrics, and all achieved excellent reliabilities for intracranial, brain, gray matter, white matter, and subcortical volumes. Superior reliability was achieved when using surface-based registration (as implemented in cortical pattern matching) compared with standard voxel-based morphometry registration and when applying a global scaling correction. Because FreeSurfer incorporates both surface-based registration and global scaling correction but also has a built-in module for vertex-based correction of the type I error rate (which cortical pattern matching does not), we opted to process the imaging data from the primary study using FreeSurfer. We report the test-retest ICCs for FreeSurfer-derived measures of cortical thickness and subcortical and ventricular volumes from the traveling subject substudy in Supplement 1.

Blood Analytes

As part of a pilot study, blood samples obtained at the BL assessment for 87 of the subjects with BL and FU MRI scans available (14 converters, 38 nonconverters, 35 control subjects) were processed using the Luminex Human DiscoveryMAP bead-based multiplex immunoassay (Luminex, Austin, Texas). Blood samples were collected in BD P100 tubes (Becton, Dickinson and Company, Franklin Lakes, New Jersey) containing ethylenediamine tetraacetate and proprietary protein stabilizers along with a mechanical separator and stored at −80°C until analysis. Analytes were transformed to *z* scores based on the means and standard deviations of the control group. Although particular cytokines may have differential functions (e.g., proinflammatory vs. anti-inflammatory) in different contexts, several included in the Luminex panel (i.e., tumor necrosis factor-α, interleukin [IL]-2, interferon-γ) are consistent activators of the M1 cytotoxic phenotype of microglia (37–40); these were summed together into an index of proinflammatory signaling. Similarly, four analytes most consistently associated with the M2 repair and regeneration phenotype of microglia (i.e., IL-10, granulocyte-macrophage colony-stimulating factor, IL-1 receptor antagonist, chemokine [C-C motif] ligand 2) (37–40) were summed together to form an index of anti-inflammatory signaling.

Statistical Analysis

Imaging measures were first transformed to annualized rates of change (ARCH) in each cortical voxel and each subcortical and ventricular region of interest (ROI), where $ROI_{ARCH} = ([ROI_{FU} - ROI_{BL}]/ROI_{BL})/Interval$ and where Interval is the time between BL and FU scans in years. This approach was preferred to repeated-measures analysis of variance (ANOVA) because the interscan interval varied across subjects (but results that were significant based on annualized rate of change were also significant using repeated measures ANOVA). Primary hypothesis testing was applied to measures of cortical thickness in FreeSurfer using the false-discovery rate (FDR) correction for multiple comparisons at the vertex level. In addition, volumetric measures of the ventricular system and subcortical nuclei were evaluated in separate ANOVAs, treating hemisphere as a repeated measure where appropriate and controlling for multiple comparisons by FDR correction. Models included age at BL, gender, site, and group (converter, nonconverter, and control) as predictors.

Secondary analyses were conducted to determine the contributions of antipsychotic drug exposure, duration of prodromal symptoms, and plasma indices of proinflammatory and anti-inflammatory cytokines to the regional measures showing evidence of differential change over time by group status. In one set of ANOVAs, converters with and without antipsychotic drug exposure during the interscan interval were compared with nonconverters with and without antipsychotic use and control subjects. In another set of ANOVAs, converters with short durations of prodromal symptoms were compared with converters with longer durations, nonconverters with short and long durations, and control subjects. A third set of analyses evaluated the linear regressions of change in cortical thickness measures on BL levels of proinflammatory and anti-inflammatory cytokines.

Results

BL Differences

There were no significant differences between converters, nonconverters, and control subjects in terms of cortical thickness or subcortical or ventricular volumes at BL, and BL measures did not vary by duration of prodrome among converters.

Rates of Change

Figure 1 shows statistical brain atlases plotting differences in the mean annualized rates of change in cortical thickness among converting CHR subjects, nonconverting CHR subjects, and healthy control subjects. In the uncorrected maps (upper panels), converters showed steeper rates of reduction in cortical thickness in a large cluster including the left and right superior frontal, middle frontal, and medial orbitofrontal gyri compared with both

control subjects and nonconverters and in smaller clusters in the right superior and inferior parietal cortex, superior temporal gyrus, and parahippocampal gyrus compared with control subjects. After applying an FDR correction thresholded at $p \leq .01$ (two-tailed), only the differences in right superior frontal, middle frontal, and medial orbitofrontal regions remained significant for both contrasts (Figure 1, lower panels). There were no significant differences in rates of change between nonconverting CHR subjects and control subjects before or after FDR correction. In parallel analyses of the volumes of subcortical and ventricular ROIs (Table 1), converters showed significantly greater expansion of the third ventricle compared with nonconverters and control subjects, who did not differ from each other.

Given that the reliabilities of thickness measures from most regions of cortex and most subcortical volumes were equivalent to or higher than that in right superior frontal and medial orbitofrontal cortex (ICCs = .92 and .68, respectively) (see Supplement 1), the topography of regions showing differential change over time in converters must primarily reflect differences in the true effect sizes rather than measurement reliability. The effect size observed in right superior frontal and medial orbitofrontal gyrus was quite large ($d = -1.0$). There were medium to large effect sizes ($d = -.30$ to $-.63$) across most of the remaining bilateral prefrontal cortex (including middle and inferior frontal gyri and frontal pole) and bilateral parahippocampal gyrus. A mask applied to the FDR-corrected p maps was used to isolate the prefrontal regions showing significantly greater thinning in converters compared with nonconverters and control subjects; the annualized rates of change for this measure and third ventricle volume were carried forward for use in subsequent analyses.

Antipsychotic Medications and Timing of FU Scan

Converters without any antipsychotic drug exposure during the interscan interval showed significantly greater reduction in right prefrontal cortex thickness and significantly greater expansion of the third ventricle compared with nonconverters with and without such exposure and with healthy control subjects but did not differ from converters with antipsychotic drug exposures on these measures (Figure 2). On average, the FU scan for converters occurred 141 days (SD = 117 days) after conversion. Neither this interval nor the duration or dosage of antipsychotic medications during the interscan interval was significantly correlated with the rate of prefrontal cortical thinning or third ventricle expansion (Table 2).

Duration of Prodrome

The CHR cases with a shorter duration of prodromal symptoms showed a significantly steeper reduction in right prefrontal thickness compared with long-duration converters, short-duration and long-duration nonconverters, and control subjects; they also showed significantly greater third ventricle expansion compared with all of the other groups except for long-duration converters (Figure 3). Long-duration converters showed a steeper rate of prefrontal thinning and third ventricular expansion compared with long-duration nonconverters and control subjects but did not differ from short-duration nonconverters on these measures.

Markers of Inflammation

Although the three groups did not differ significantly from each other in mean levels of proinflammatory [$F = .95$, $p = .39$] or anti-inflammatory [$F = .98$, $p = .38$] cytokines at BL, the rate of prefrontal cortical thinning was significantly associated with higher levels of proinflammatory markers in the sample overall, and this inverse correlation was significantly greater among converters than among nonconverters and control subjects (Table 3). Proinflammatory cytokines were not associated with third ventricular expansion, and anti-inflammatory cytokines were not associated with rate of change in either of the MRI measures.

Discussion

Individuals at CHR who develop psychosis show a steeper rate of gray matter loss in right superior frontal, middle frontal, and

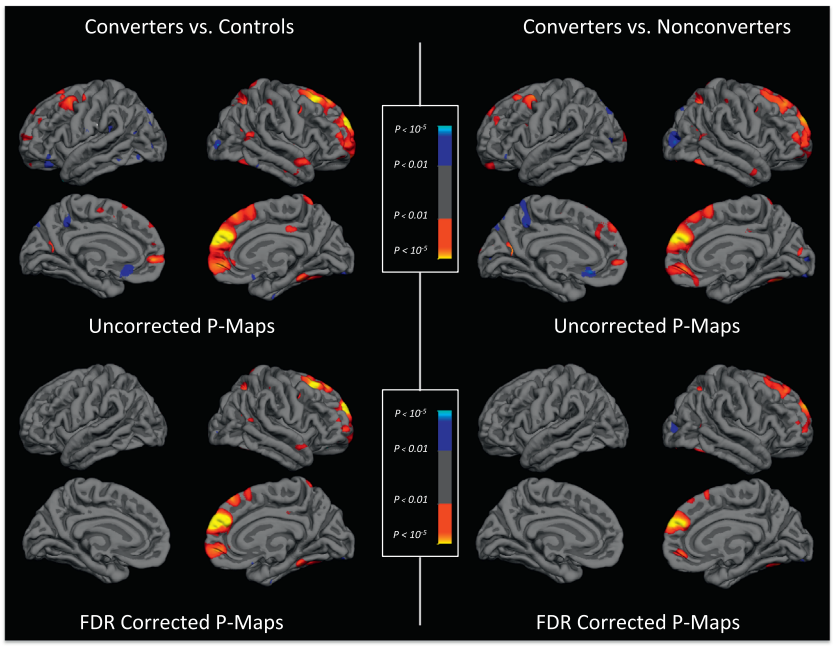

Figure 1. Statistical brain atlases plotting differences in the mean annualized rates of change in cortical thickness among converting clinical high risk subjects ($n = 35$), nonconverting clinical high risk subjects ($n = 239$), and healthy control subjects ($n = 135$). Panels on the left show differences between converters and control subjects, and panels on the right show differences between converters and nonconverters. In the uncorrected maps (upper panels), compared with both nonconverters and control subjects, converters showed greater thinning (warmer colors) in left and right superior frontal, middle frontal, and medial orbitofrontal gyri and in the right superior and inferior parietal cortex, superior temporal gyrus, and parahippocampal gyrus. After applying an FDR correction ($p \leq .01$; lower panels), only the differences in right superior frontal, middle frontal, and medial orbitofrontal regions remained significant for both contrasts. The small clusters showing greater expansion (cooler colors) in the converters compared with control subjects in the uncorrected maps did not survive correction for multiple comparisons. There were no differences between nonconverters and control subjects before or after FDR correction. FDR, false-discovery rate.

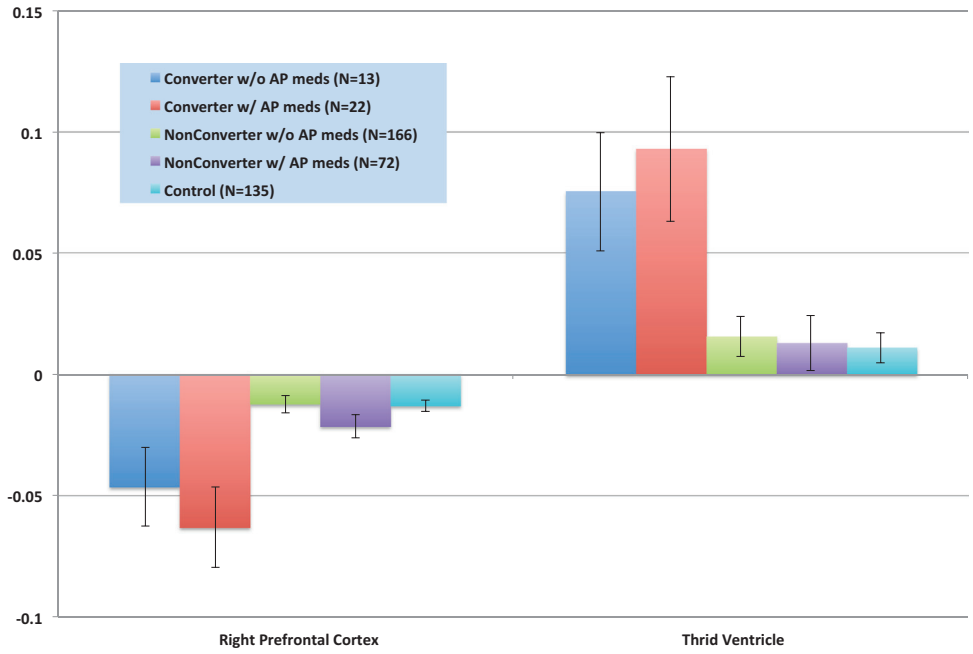

Figure 2. Mean annualized rates of change in right prefrontal cortex thickness and third ventricle volume by antipsychotic (AP) drug exposure during the interscan interval. Group differences were significant for both variables [$F = 7.46$, $p = .000008$ for right prefrontal cortex; $F = 3.74$, $p = .005$ for third ventricle]. Converters with and without AP medications showed significantly steeper reduction in right prefrontal thickness and significantly greater expansion of the third ventricle compared with nonconverters with and without AP medications and control subjects.

medial orbitofrontal cortex and a greater rate of expansion of the third ventricle compared with at-risk individuals who do not convert and healthy comparison subjects. These effects were present among subjects who had not received antipsychotic medications during the interscan interval, demonstrating that the differential tissue loss associated with onset of psychosis is not explained by exposure to antipsychotic drugs. This finding represents a critical advance, given that antipsychotics complicate the interpretation of progressive brain changes among patients in the first episode of psychosis (13–16). A similar result was observed among unmedicated familial high-risk subjects who showed increasing symptom severity (41). It is possible that progressive gray matter reduction is linked in some way to the pathophysiology of onset of psychosis.

Prior studies of CHR cases reported steeper reductions in prefrontal, superior temporal, and parahippocampal regions among converters compared with nonconverters (1–7). The sample sizes in those studies were significantly smaller than the sample sizes in the present study, and none employed a voxel-based or vertex-based correction for multiple comparisons. Because the traveling subjects substudy revealed comparably high test-retest reliability across most cortical and subcortical regions, the topographical pattern of differential change in this study primarily reflects regional variation in effect size, which was sufficiently high in right superior and medial prefrontal regions and in the third ventricle to survive rigorous control for multiple comparisons throughout the brain. This study strongly confirms prior evidence of differential tissue loss in prefrontal cortex among CHR converters to psychosis, with a topography highly similar to that in the only prior study using surface-based anatomic comparison (2). The primary advantage of the vertex-based, FDR-corrected threshold employed in this study is that it protects against false-positive findings given the number of tests conducted and distribution of observed *p* values. We can have high confidence that the effects that were significant are true-positive findings. Adoption of this conservative threshold might also lead to some false-negative results. There were medium to large effect sizes across most of the remaining bilateral prefrontal

Table 2. Correlations of Annualized Rates of Change in Right PFC Thickness and Third Ventricle Volume with Temporal Factors

	Overall Sample			Converters Only		
Variable	*n*	Right PFC	Third Ventricle	*n*	Right PFC	Third Ventricle
Age at BL Scan	409	.01	.01	35	−.16	.22
Interscan Interval	409	0.12[a]	−.09[b]	35	.46[a]	−.46[a]
Duration of Prodrome[c]	251	.13[b]	.04	35	.36[b]	−.31
Duration of AP Medications[c]	273	−.03	−.03	35	.11	−.20
Dosage of AP Medications[c]	273	−.01	−.05	35	.07	−.11
Interval from Conversion to Scan	NA	NA	NA	35	.15	−.23

AP, antipsychotic; BL, baseline; NA, not available; PFC, prefrontal cortex.
[a] $p < .01$.
[b] $p < .05$.
[c] Clinical high risk subjects only.

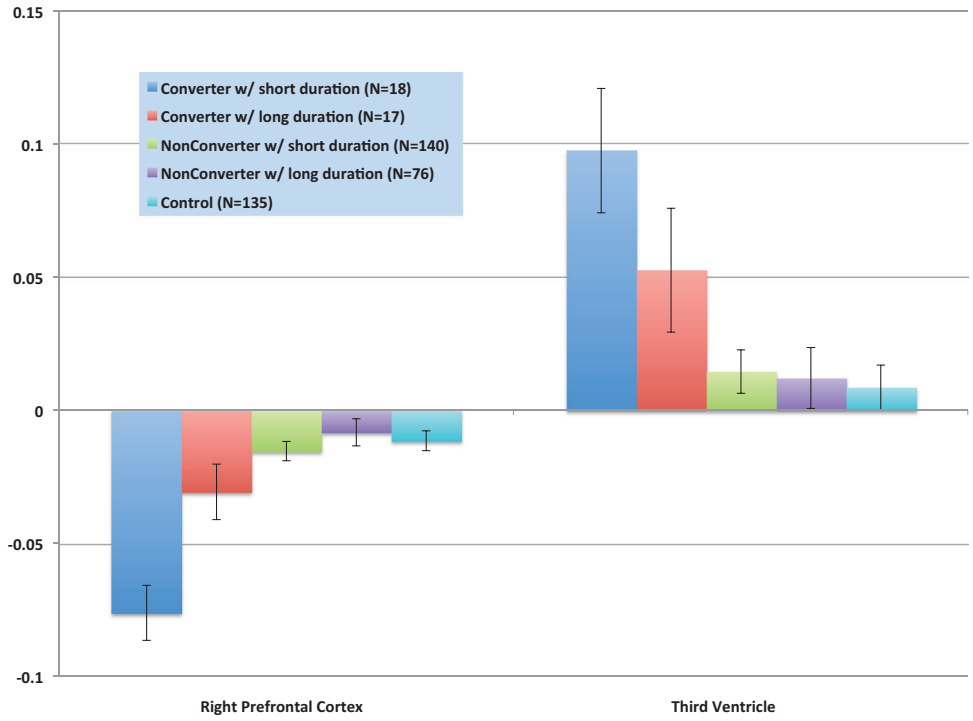

Figure 3. Mean annualized rates of change in right prefrontal cortex thickness and third ventricle volume by duration of prodromal symptoms. Group differences were significant for both variables [$F = 9.68$, $p = .0000002$ for right prefrontal cortex; $F = 3.87$, $p = .004$ for third ventricle]. Converters with short durations showed significantly steeper reduction in right prefrontal thickness compared with long-duration converters, short-duration and long-duration nonconverters, and control subjects; short-duration converters also showed significantly greater third ventricle expansion compared with all of the groups except for long-duration converters. Converters with long durations showed significantly steeper reduction in right prefrontal thickness and significantly greater expansion of the third ventricle compared with long-duration nonconverters and control subjects.

cortex (including left and right middle and inferior frontal gyri and frontal pole) and bilateral parahippocampal gyrus as well as in some circumscribed regions of temporal and parietal cortex, overlapping the regions showing differential change in prior studies (1–7).

Higher levels of a plasma-based aggregate index of proinflammatory cytokines at BL were strongly predictive of steeper rates of gray matter reduction in right prefrontal cortex among CHR cases who converted to psychosis. Given that peripheral cytokines can affect brain function (42), and because the cytokines included in the proinflammatory index are potent activators of the M1 cytotoxic phenotype of microglia that result in synaptic pruning and dendritic retraction (37–40), it is plausible to hypothesize a mechanistic link between neuroinflammation (i.e., microglial activation) and progressive gray matter loss in individuals who develop psychosis, a hypothesis that should be tested using more direct indicators of neuroinflammatory processes in CHR subjects.

Table 3. Correlations of Annualized Rates of Change in Right PFC Thickness and Third Ventricle Volume with Serum Inflammatory Indices by Outcome Group

Region	Group	*n*	Proinflammatory Cytokines[a]	Anti-inflammatory Cytokines
Right PFC	Control	35	.12	−.05
	Nonconverter	38	−.32[b]	−.02
	Converter	14	−.65[c]	.38
	Overall	87	−.37[c]	.06
Third Ventricle	Control	35	−.18	−.10
	Nonconverter	38	.09	.06
	Converter	14	−.15	−.41
	Overall	87	−.02	−.10

PFC, prefrontal cortex.

[a]The relationship between proinflammatory cytokines and right PFC contraction was significantly greater in converters than in nonconverters and control subjects [$F_{3,83} = 10.1$, $p = .00001$].

[b]$p < .05$.

[c]$p < .01$.

The steeper rate of decline in right prefrontal cortex and expansion of the third ventricle were more pronounced among converters with shorter durations than converters with longer durations, but the long-duration converters also showed differential change compared with nonconverters and control subjects. This pattern suggests that a steeper rate of tissue loss in these regions, or the factors promoting it, may help to trigger an earlier onset of psychosis. Because there were no significant differences between converters, nonconverters, and control subjects in cortical thickness or subcortical volumes at the BL assessment controlling for multiple comparisons, this finding suggests that the reductions in gray matter emerge around the time of onset of psychosis, rather than earlier, among CHR cases. Some, but not all, prior studies have detected anatomic differences at BL between CHR individuals who do and do not later convert, despite the use of much smaller sample sizes than in this study, by focusing on a small number of ROIs or by otherwise employing a less conservative statistical threshold (1,3,4,43–61). Nevertheless, the CHR criteria are sensitive primarily to acute-onset forms of psychosis and may underrepresent individuals with more insidious onsets,

who might manifest loss of gray matter volume at earlier assessment points because of early life risk exposures, such as fetal hypoxia (62). The extent to which future converters manifest anatomic deficits at BL could also potentially reflect the relative proportions of converters with insidious versus acute onsets in the sample under study.

The question arises as to whether gray matter reduction per se is a causal factor in onset of psychosis. Given that the distributions of cortical gray matter volumes among patients with schizophrenia and healthy control subjects overlap by 50%–75%, it does not appear that there is a critical threshold of cortical thickness (in any one region or combination of regions) below which psychosis develops. Nevertheless, there is likely to be a threshold of integrated synaptic activity and regional functional connectivity that does discriminate individuals in a psychotic state from others. Gray matter reduction is perhaps best conceptualized as a marker of a set of processes that contributes to reductions in integrated synaptic activity and functional connectivity, which might represent a proximal sufficient mechanism of psychosis onset. Although there are likely mechanisms that disrupt synaptic activity and functional connectivity in psychosis-relevant networks without affecting cortical volume, gray matter reduction is nevertheless an observable and reliably measured phenomenon that appears to play a role in a significant proportion of cases and provides insight into the network of brain regions likely to participate in psychosis onset in general.

In this study as well as in all prior longitudinal studies of CHR cases (1–7), the FU scans for converters occurred after the point of conversion. Although the change in gray matter volume was not correlated with the interval between onset of psychosis and the second scan, it is not yet known whether significant change occurs before onset of psychosis. However, it is reassuring that the absolute magnitude of change in the right prefrontal ROI among the four converters who had FU scans before the point of conversion (i.e., mean $\pm$ SD = $-.11 \pm .08$ mm) was comparable to the magnitude of change among cases whose FU scans occurred after conversion ($-.12 \pm .11$ mm) and was greater in magnitude compared with nonconverters ($-.05 \pm .13$ mm) and control subjects ($-.05 \pm .10$ mm). When these four cases were included with cases with FU scans performed after conversion, converters continued to show significantly greater contraction of right prefrontal cortex [$F_{2,401} = 12.66$, $p = .000004$] compared with nonconverters and control subjects. Given that in this study and in a prior large study of prodromal youth at these same sites (63) >70% of the conversions had occurred by 10 months, future studies are warranted to time MRI assessments at 2-month intervals from BL to ensure at least two assessment points before conversion for most cases.

In conclusion, individuals with CHR who convert to psychosis show a steeper rate of thinning in prefrontal cortex, an effect that is independent of exposure to antipsychotic drugs and is predicted by plasma analytes indicative of an inflammatory process. Future work is encouraged to confirm a neuroinflammatory signature in the regions showing gray matter loss and to determine whether inflammation precedes and predicts the gray matter loss or is a consequence of it.

This work was supported by a collaborative U01 award from the National Institute of Mental Health (NIMH) at the National Institutes of Health (Grant Nos. MH081902 [TDC], MH081857 [BC], MH081988 [EW], MH081928 [LJS], MH082004 [DP], MH082022 [KC], MH081984 [JA], and MH066160 [SWW]) and NIMH Grant No. P50 MH066286 (CEB), NIMH Grant No. P50 MH080272, and the Commonwealth of Massachusetts (Grant No. SCDMH82101008006 [LJS]).

The authors report no biomedical financial interests or potential conflicts of interest.

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Emory University: Hanan Trotman; Xiaoping Hu; Lei Zhou; Stephan Hamann; Arthur Ryan; Erica Duncan; Joy Brasfield; Anna Pless; Ben Perlow; Dan Shapiro; Sandy Goulding; Carrie Holtzman; Allison MacDonald; Erin Jones; David Lui;

Harvard University/Beth Israel Deaconess Medical Center: Kristen Woodberry; Anthony Giuliano; Michelle Friedman-Yakoobian; William Stone; Heidi Thermenos; Margaret Niznikiewicz; Robert McCarley; Linda Tucker; Corin Pilo; Maryan Picard; Benjamin Brent; Ann Cousins; Raquelle Mesholam-Gately; Andrea Gnong Granato; Janine Rodenhiser-Hill; Joanne Wojcik; Lauren Gibson; Richard Juelich; Danbee Kim; Grace Min; Rachel Serur; Beril Yaffe;

Zucker Hillside Hospital: Andrea Auther; Danielle McLaughlin; Doreen Olvet; Peter Kingsley; Ricardo Carrion; Gary Brucato; Ruth Olsen; Tricia Taylor; Rita Barsky; Stephanie Snyder; Miranda Farabaugh; Jeremy Chang; Kristin Candan;

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Supplementary material cited in this article is available online at http://dx.doi.org/10.1016/j.biopsych.2014.05.023.

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