Time-Lapse Mapping of Cortical Changes in Schizophrenia with Different Treatments

Using time-lapse maps, we visualized the dynamics of schizophrenia progression, revealing spreading cortical changes that depend on the type of antipsychotic treatment. Dynamic, 4-dimensional models of disease progression were created from 4 repeated high-resolution brain magnetic resonance imaging scans of 36 first-episode schizophrenia patients (30 men/6 women; mean age: 24.2 ± 5.1 SD years) randomized to haloperidol (HAL) (n = 15) or olanzapine (OLZ) treatment (n = 21), imaged at baseline, 3, 6, and 12 months (144 scans). Based on surface-based cortical models and point-by-point measures of gray matter volume, we generated time-lapse maps for each treatment. Disease trajectories differed for atypical versus typical neuroleptic drugs. A rapidly advancing parietal-to-frontal deficit trajectory, in HAL-treated patients, mirrored normal cortical maturation but greatly intensified. The disease trajectory advanced even after symptom normalization, involving the frontal cortex within 12 months with typical drug treatment. Areas with fastest tissue loss shifted anteriorly in the first year of psychosis. This trajectory was not seen with OLZ. Whether this association reflects either reduced neurotoxicity or neuroprotection cannot be addressed with neuroimaging; changes may relate to glial rather than neural components. These maps revise current models of disease progression, revealing spreading cortical changes that depend on the type of antipsychotic treatment. Dynamic, 4-dimensional models of disease progression were created from 4 repeated high-resolution brain magnetic resonance imaging scans of 36 first-episode schizophrenia patients (30 men/6 women; mean age: 24.2 ± 5.1 SD years) randomized to haloperidol (HAL) (n = 15) or olanzapine (OLZ) treatment (n = 21), imaged at baseline, 3, 6, and 12 months (144 scans). Based on surface-based cortical models and point-by-point measures of gray matter volume, we generated time-lapse maps for each treatment. Disease trajectories differed for atypical versus typical neuroleptic drugs. A rapidly advancing parietal-to-frontal deficit trajectory, in HAL-treated patients, mirrored normal cortical maturation but greatly intensified. The disease trajectory advanced even after symptom normalization, involving the frontal cortex within 12 months with typical drug treatment. Areas with fastest tissue loss shifted anteriorly in the first year of psychosis. This trajectory was not seen with OLZ. Whether this association reflects either reduced neurotoxicity or neuroprotection cannot be addressed with neuroimaging; changes may relate to glial rather than neural components. These maps revise current models of schizophrenia progression; due to power limitations, the findings require confirmation in a sample large enough to model group × time interactions.

Keywords: cortex, development, imaging, neurotoxicity, schizophrenia

Introduction

Schizophrenia is a debilitating neuropsychiatric disorder, which typically manifests in the late teens or early twenties, and affects 0.5–1% of the population worldwide (Goldner et al. 2002). Characteristic symptoms include auditory hallucinations, sensory disturbances and disordered thinking, depression and social withdrawal. The neurobiological basis of schizophrenia is of great interest for therapeutic development, but is still largely unknown. Most investigators agree that there is a predominantly genetic susceptibility to the illness, but stressors later in life (e.g., glucocorticoids, substance use, or viral factors) may be required to promote psychosis onset (Weinberger and McClure 2002). As the illness proceeds, patients rapidly lose gray matter, particularly in frontal and temporal lobes (Gur et al. 1998; Lieberman et al. 2003). In severe, early-onset schizophrenia, some studies have found that gray matter volume reductions progress in a parietal-to-frontal wave mimicking the normal cortical maturation pattern, but accelerated (Thompson et al. 2001; Gogtay et al. 2004; Vidal et al. 2006). Other studies have disputed these findings, both in terms of whether there is progression or not, and where it is maximal (see DeLisi et al. 1997; Mathalon et al. 2001; and Arango and Kahn 2008, for a discussion). Both Pantelis et al. (2003) and Job et al. (2005) suggest that at least in the very earliest stages of adult-onset psychosis there are replicated changes in frontal and temporal lobes rather than the parietal lobes, and in a high-risk group, Job et al. (2005) also found progressive reductions in gray matter density in the right parietal lobes, among other regions. Gray matter loss may reflect dysregulated or exaggerated gray matter pruning, or a limited neurodegenerative process (Lieberman 1999). PARadoxically, histologic studies in schizophrenia find prefrontal cortical volume reductions but no classical signs of neurodegeneration such as neuronal loss or gliosis (Selemion et al. 1999; Harrison and Lewis 2003). The volume deficit may reflect: 1) exaggerated dendritic or synaptic pruning (Keshavan et al. 1994; McGlashan and Hoffman 2000), 2) impaired myelination, which may explain the reduced cortical neuropil and thinner cortex on magnetic resonance imaging (MRI) (Bartzokis et al. 2003), 3) neuroplastic adaptations to the experience of being psychotic (Weinberger and McClure 2002), 4) apoptotic effects on cell processes and synapses (Glantz et al. 2006), and/or 5) neurotoxic effects of first-generation antipsychotic medications (Reinke et al. 2004). Pharmacological agents are unlikely to be the sole cause of these progressive changes, as medication-naïve subjects show accelerated frontal tissue loss before psychosis onset (Pantelis et al. 2003). Patients’ healthy first-degree relatives show mild gray matter reductions that correlate with the presence of known schizophrenia risk genes (Cannon et al. 2005; e.g., DISC1/TRAX haplotypes), but it is unknown whether these deficits worsen with time.

In a recent clinical trial (Lieberman et al. 2003), patients treated with the typical antipsychotic drug, haloperidol (HAL), showed progressive gray matter loss, whereas olanzapine (OLZ)-treated patients did not; OLZ may be neuroprotective, less neurotoxic, or both (Molina 2005). HAL blocks D₂-type dopamine receptors, whereas second-generation antipsychotics have a so-called “atypical” neuropharmacological...
profile that includes effects at serotonin 5-HT2A, histamine H1, and adrenergic α1 receptors, in addition to dopamine (D2) receptor antagonism (Kapur and Seeman 2000). In many but not all studies, atypical antipsychotics are more effective for managing negative symptoms and produce less extrapyramidal (Parkinsonian) side effects, but which treatment is optimal is hotly debated (Molina 2005). This paper presents time-varying maps of disease progression for the 2 major types of antipsychotic treatment, revealing that they differentially resist the neuroanatomical advance of schizophrenia, long after symptoms have been alleviated.

Methods

Summary

Dynamic maps of disease progression were created by applying a novel type of image analysis, called “cortical pattern matching” (Thompson et al. 2004), to brain MRI scans of patients with schizophrenia. Acutely psychotic first-episode schizophrenia patients were randomized to one of 2 antipsychotic drugs with different mechanisms of action (HAL and OLZ) and identically scanned with MRI on 4 occasions (0, 3, 6, and 12 months). We compared the anatomical trajectory of disease progression for each treatment, using a well-validated cortical mapping approach that we developed and have used previously to track cortical alterations in Alzheimer’s disease, normal development (Gogtay et al. 2004), childhood-onset schizophrenia (Thompson et al. 2001; Vidal et al. 2005), in neuretropaminergic users, in HIV/AIDS, epilepsy, velocardiofacial syndrome, Williams syndrome, bipolar illness, and late-onset depression (see Thompson et al. 2004 for references). To understand the clinical significance of the observed changes, we also correlated these progressive brain changes with standard assessments of therapeutic efficacy—positive, negative, and overall symptoms of schizophrenia, and quality of life scores (QLS).

Subjects: Inclusion and Exclusion Criteria

We analyzed the brain MRI scans of a subsample of patients from a previously published study (Lieberman et al. 2005). Briefly, Lieberman et al. (2005) conducted a double-blind, randomized, multicenter study of treatment efficacy in 263 patients with first-episode psychosis, meeting Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria for schizophrenia, schizophreniform, or schizoaffective disorder. Patients were randomized to OLZ (5–20 mg/day) or HAL (2–20 mg/day) at 14 academic medical centers (11 in the United States, 1 in Canada, 1 in the Netherlands, and 1 in England). Patients who presented to clinical services (inpatient, emergency, and outpatient) for evaluation and treatment of a first episode of psychosis were enrolled in the study if they met the following inclusion and exclusion criteria: age 16–40 years; onset of psychotic symptoms before age 35 years; diagnosis of schizophrenia, schizophreniform, or schizoaffective disorder according to DSM-IV criteria (as assessed with the Structured Clinical Interview for DSM-IV, Research Version); previous cumulative antipsychotic drug treatment of no more than 16 weeks, or treatment with clozapine at any time in the patient’s lifetime; no current substance dependence (except caffeine and nicotine) by DSM-IV within 1 month before study entry; no current indication of serious suicidal risk; female subjects not pregnant or nursing; premorbid IQ of 70 or more; no requirement of concurrent treatment with antidepressants, benzodiazepines (except as allowed for agitation and control of extrapyramidal symptoms), antiretroviral agents, or other antipsychotic drugs at study entry; and no contraindication for neuroimaging per current regulations from the local regulatory agency (e.g., metal prostheses). In addition, no subject developed substance dependence during the study, which could otherwise have been a confound influencing withdrawal from the study. Each patient (or a patient’s authorized legal representative) had to understand the nature of the study and sign an informed consent document. Each site’s institutional review board approved the study. By way of clarification, the patients examined here were not a subset of the patients in the recent CATIE trial (Clinical Antipsychotic Trials of Intervention Effectiveness; Keefe et al. 2007; Lieberman 2007). The CATIE study specifically excluded first-episode patients, and the 2 studies were not contemporaneous in time—the current study, with the codename HGD, preceded CATIE and had finished by the time CATIE started enrollment.

Study Design and Procedures

Patients were randomized to double-blind treatment with OLZ or HAL for up to 104 weeks. Dosage of HAL was not high compared with OLZ; the therapeutic range for HAL is 2–20 mg/day and for OLZ, 5–20 or approximately 30 mg/day. The mean modal doses in the study were approximately 5 mg/day for HAL and 10 mg/day for OLZ. Permitted concomitant medications, listed in Lieberman et al. (2005), were allowed only for a cumulative duration of no more than 21 days. Antidepressants (except fluoxetine hydrochloride) and/or mood stabilizers were not allowed in the first 12 weeks of the study but could be added if clinically indicated thereafter. Psychopathology and neurocognitive outcomes were the other primary assessments of efficacy. Psychopathology was assessed at each follow-up visit by the 36-item Positive and Negative Syndrome Scale (PANSS; 1–7 severity score; Kay et al. 1987) and QLS were assessed as described previously (Lieberman et al. 2005; Keefe et al. 2004).

MRI Scanning

Patients underwent MRI scans at weeks 0 (baseline), 12, 24, 52, and 104. A total of 161 (of 263) patients had baseline and at least one postbaseline MRI; of these, 40 patients had MRI scans at all time points but 80 had scans at the first 4 time points (0, 12, 24, and 52 weeks). We chose to examine the disease trajectory over the first 4 time points (i.e., to 1 year rather than 2 years) as the available sample size was twice as large. Because of the relatively small numbers of subjects at some scanning sites, we included only scans acquired at a single site (Duke University) from patients ascertained from the University of North Carolina and Duke University, which comprised the largest number of subjects in the study. This avoided 1 unmodeled confounds incurred by combining data from multiple scanners; 2) the need to model cross-scan differences in image contrast-to-noise ratio and 3D spatial calibration, which can influence tissue volume estimates. The remaining 36 subjects (30 men/6 women) with MRI scans at all 4 time points had a mean age of 24.2 ± 5.1 SD years (ages reported at baseline scan). They included 21 subjects (17M/4F) randomized to OLZ (mean age: 24.3 ± 5.5 SD years) and 15 subjects (13M/2F) randomized to HAL (mean age: 23.9 ± 4.8 SD years). All MRI studies were performed (by one of us, C.C.) on a General Electric Signa 1.5-Tesla MRI scanner at the Center for Advanced Magnetic Resonance Development, Department of Radiology, Duke University Medical Center, Durham, NC. The imaging protocol included a 3-dimensional $T_1$-weighted, inversion recovery-prepared spoiled gradient echo volumetric image (0.94 x 0.94 x 1.50 mm, axial direction) Quality-control scans were performed twice a month with standardized imaging phantoms, to ensure geometrical calibration and stability over time. The image acquisition remained blinded throughout the trial. Each data set was processed as follows.

Image Processing and Analysis

Serial images acquired on the 4 occasions across the 1-year time-span were processed as follows (Fig. 1 shows a flow-chart). Briefly, image intensity nonuniformity correction was applied to each image using a regularized tricubic B-spline approach (Shattuck et al. 2001). Images were normalized by transforming them to a standard 3D stereotaxic space, in a 2-step process that retained information on brain change over time. First, each baseline scan was linearly aligned (registered) to a standard brain imaging template (the International Consortium for Brain Mapping nonlinear average brain template, ICBM53; Evans et al. 1996) with automated image registration software (Collins et al. 1995). Follow-up scans were then rigidly aligned (i.e., without allowing scaling) to the baseline scan from the same subject (Collins et al. 1995). These mutually registered scans for each patient were then linearly mapped into ICBM space by combining the intrapatient transform with the previously computed transform to stereotaxic space. This procedure allows each individual’s brain to be matched in a common space but keeps global differences in brain size and shape intact. Automated
tissue segmentation was performed on each data set to classify voxels based on signal intensity as most representative of gray matter, white matter, cerebrospinal fluid (CSF) or extracerebral background class (Thompson et al. 2004). A Gaussian mixture distribution reflecting the statistical variability of intensities in each image was first computed before assigning each voxel to the class with the highest probability. Gray matter maps were retained for further analysis, whereas nonbrain tissue such as scalp and orbits were removed from the spatially transformed, tissue-segmented images. A 3-dimensional cortical surface model was extracted (MacDonald 1998; Thompson et al. 2001, 2004) for each subject and time point, by creating a mesh-like surface that is continuously deformed to fit a threshold intensity value of the brain image that best differentiated cortical CSF from underlying cortical gray matter (Thompson et al. 2004).

Cortical Pattern Matching
An image analysis technique, known as cortical pattern matching (Thompson et al. 2004), was used to better localize disease effects on cortical anatomy over time, and increase the power to detect systematic changes. The approach models, and controls for, gyral pattern variations across subjects, visualize average maps of cortical change in a population, and encode their variance and group differences. From each subject's cortical models at different time points, a 3D deformation vector field was computed measuring brain surface shape change across the time interval (Thompson et al. 2001). This accommodates any brain shape changes when comparing cortical gray matter within a subject across time. The deformation reconfigures the earlier cortex into the shape of the later one, matching the entire gyral patterns and cortical surfaces in the pair of 3D image sets.

We note that all follow-up scans were first registered to the corresponding baseline scan from the same subject, using a rigid-body (6-parameter) transformation. Next, a single 9-parameter transformation (with scaling) was used to align the baseline scan (and all coregistered follow-up scans) to the ICBM standard brain template. The exact same transform, computed from the baseline scan, was identically applied to all the follow-up scans from the same subject.

Figure 1. Steps used to create cortical maps. All 144 brain MRI images were registered to a standard space, edited to remove extracerebral tissues, and processed to create maps of cortical gray matter density (bottom right). Sulcal landmarks were also traced on cortical surfaces extracted from the scans. Using these sulcal landmarks as anchors, well-resolved average models of the cortex were created for each group (bottom left), allowing gray matter measures to be compared across time and pooled across homologous cortical areas (see Methods).
Mapping Schizophrenia Progression
across treatment groups.

data across time, were also computed for averaging and comparison
time and then also across subjects. This cortical matching localizes
matter density measures from homologous cortical regions first across
high-dimensional elastic matching of cortical patterns associated gray
Given the cross-subject anatomic variability in some cortical regions,
measures). 3D maps of GM density were mapped onto the correspond-
surface model (see Thompson et al. 2004, for many studies using similar

distribution of gray matter across subjects. This was defined as the
density,'' used in many previous studies to compare the spatial
quantify local gray matter, we used a measure termed ''gray matter
HAL and OLZ treatment groups, at each time point (see Fig. 2). To
Average Gray Matter Map Construction
an average 3D cortical gray matter map was computed for each of the
subjects in the study, in addition to the deformation that
all the subjects in the study, and comparing these maps across time points.

Statistical Maps of Gray Matter Loss
Statistical maps were generated indicating locally the degree to which
gray matter density 1) changed over time (relative to baseline) in each
treatment group (Figs 3-5), 2) differed by treatment group (HAL vs.
OLZ) at each of the time points, and 3) was statistically linked with
clinical outcome measures (total PANSS, positive, negative, and general
psychopathology scores; Lieberman et al. 2005). To do this, at each
cortical point, a multiple regression was run to assess whether the gray
matter density at that point depended on the covariate of interest (e.g.,
treatment, time point, or test scores). The $P$ value describing the
significance of this linkage was plotted at each cortical point using
a color code to produce a statistical map. Specifically, we created maps
of the following 2 kinds:

1) Maps of gray matter loss over time, per treatment group (Figs 3-5),
2) Maps of the differences between treatment groups in gray matter
loss at each specific time (Fig. 7).

In the maps of gray matter loss over time, the $P$ value at each point is
derived from a paired Student’s $t$ statistic comparing follow-up to
baseline gray matter at each surface point. Because we could not be
sure a priori whether the changes would be heavily concentrated
between the first and second time point, or roughly linear over time, or
asymptotically slowing according to a nonlinear trajectory in time, we
opted to statistically gauge any loss relative to the gray matter
distribution at baseline, creating a time-series of statistical maps versus
baseline. This assesses all deficits at each time point relative to baseline.
An alternative approach, to assess additive sequential loss, might be to
capture each scan with the scan immediately before it, rather than
with baseline, but we preferred to use the baseline as a reference for
every time point so that the significance of the cumulative deficits
could be established. In Figure 3, the significance of the loss pertains to
the paired $t$ statistic (Fig. 4) comparing follow-up to baseline gray
matter at each surface point, within each treatment group.

By contrast, in the maps of the differences between treatment groups
in gray matter loss (Fig. 7), we aggregated the scans in each treatment
group at a specific time point. Then, at that time point, we created
$t$ statistics (2-tailed) to assess the significance of any difference in group
means for gray matter density at that time point. From those statistics,
$P$ values were plotted on the average surface model from all subjects.
We note that the $P$ values in Figure 3 and 5 refer to the effect of time
within a group, but the $P$ values in Figure 7 refer to the effect of group
at a specific time. We chose not to fit a general time-varying model
through all time points and groups, as we could not be sure a priori
whether the trajectories would be linear, nonlinear, or with deficits
occurring primarily between T1 and T2. Because of this, we took
a more agnostic approach in which groups were compared at each
time point, and time points were directly compared within group. If
a trajectory of a certain analytical form (e.g., linear or quadratic)
had been hypothesized based on prior independent data, alternative
approaches may have been preferable, and we could have pooled
variance estimators across all scans to regress the effect of time, group,
and their interaction. Instead, we opted to show the associated $P$ value
for the effect of group difference at each time point, as in prior work
modeling gray matter trajectories in development (Gogtay et al. 2004)
and Alzheimer’s disease (Thompson et al. 2003).

Matching Cortical Anatomy across Subjects
A second deformation was computed that matches gyral patterns across
all the subjects in the study, in addition to the deformation that
matches anatomy over time. This allows data to be averaged across
a group of subjects and compared against corresponding cortical
regions (Thompson et al. 2004). A set of sulcal landmarks per brain is
used to constrain the mapping of one cortex onto another. This
associates corresponding cortical regions across subjects. Following 3D
hemispheric reconstruction, 38 sulci per hemisphere were traced
according to a protocol with established inter- and intrarater reliability.
A group-average cortical map was computed. The parameterized,
flattened hemispheric surfaces were warped to the average sulcal
representations assuring explicit matching of corresponding gyri, as far
as possible, before averaging of data on gray matter distribution across
subjects, and comparing these maps across time points.

Multiple Comparisons Correction
The spatial maps (uncorrected) visualize the spatial patterns of gray
matter deficits, but permutation methods are used to assess the overall
significance of the statistical maps and to correct for multiple
comparisons. In general in neuroimaging studies, it is necessary to
ascribe a significance value to the overall pattern of effects in the map,
bearing in mind that with so many statistical tests conducted each point
on the cortical surface, even under the null hypothesis of no effects, on
average 5% of the point on the cortex would show a significance value
of $P < 0.05$. The overall $P$ value in permutation testing was computed by
comparing the number of voxels in the suprathreshold set (the
suprathreshold cluster was defined as voxels with significance $P$ value
less than 0.01) in the true labeling to the permutation distribution
(Nichols and Holmes 2001). As in several prior cortical mapping and
other imaging studies (e.g., Thompson et al. 2005; Chiang et al. 2007),
Permutation tests were conducted on the suprathreshold count of statistics with effect sizes at the voxel level greater than $P = 0.01$ uncorrected, and a corrected global $P$ value for the pattern of effects in the overall map was based on the quantiles of the null distribution for the suprathreshold count. This provides an approximate corrected $P$ value for the effects in the overall map, and intuitively it may be interpreted as the proportion of randomized maps that "beat" the true map. The number of permutations $N$ was chosen to control the standard error $SE_P$ of omnibus probability $P$, which follows a binomial distribution $B(N, P)$ with $SE_P = \sqrt{p(1-p)/N}$ (Edgington 1995). We selected $N > 8000$ tests out of the total number of possible permutations ($\approx 10^{25}$) such that the approximate margin of error (95% confidence interval) for $P$ was around 5% of $P$, and 0.05 was chosen as the significance level. We used permutation rather than Gaussian field theory to avoid making assumptions about the spatial covariance of the residuals (see Thompson et al. 2004). In each case, the covariate of interest was permuted 100,000 times on an SGI Reality Monster supercomputer with 32 internal R10000 processors, and a null distribution was developed for the area of the average cortex with statistics above a fixed threshold in the significance maps. An algorithm was then applied to report the significance probability for the statistical effects in each map as a whole (Thompson et al. 2004), after

Figure 2. Average cortical gray matter maps. Average maps of cortical gray matter density are shown for the HAL-treated and OLZ-treated groups. Five different views are shown (top, left, and right lateral, right and left medial), for each treatment group at each time point (the corpus callosum is shown in white). Changes are too subtle to be visually evident, but these average maps are the basis for computing the maps of rates of change over time (Figs 3–6), and treatment differences (Fig. 7), which come from comparing maps in different rows of this figure.
appropriate correction for multiple comparisons. Separate maps were made in each treatment group to show the significance and average rates of loss in the interval between the baseline scan and each subsequent time point (Figs. 5 and 6), and significant differences between treatment groups (Fig. 7).

Results

Trajectory of Gray Matter Deficits with HAL Treatment

In HAL-treated patients, a dynamically spreading wave of significant gray matter loss was detected when each set of subsequent scans was compared with the baseline scan (Fig. 3). Time-lapse video sequences show these changes emerging over time, and can be viewed on the Internet at: http://www.loni.ucla.edu/~thompson/MOVIES/HGDH/sz.html.

Figure 4 shows the effect sizes for these brain changes, as maps of Student’s \( t \) statistics, for the gray matter loss in each group. They compare the cortical change occurring over 1 year with the standard error in the changes within each group. As \( t \) statistics greater than 2 are significant at the voxel level, they show that the frontal cortical losses in the HAL group are almost twice as high as the significance threshold, whereas the diffuse losses in the OLZ group have numerically lower effect sizes in a more posterior parietal anatomical pattern at the midline.

Progressive gray matter reduction began in lateral parietal–temporal cortices by 3 months (Fig. 5), spreading into the dorsolateral, medial frontal, and prefrontal cortices by 6 months, and involving most of the frontal cortex by 1 year after the first psychotic episode. This trajectory was comparable in both brain hemispheres, and intensified over time.

On the medial wall of each hemisphere, posterior cingulate deficits spread anteriorly to include the rest of the limbic cortex by 6 months, and then swept into the frontal and prefrontal cortices, all with widespread significant tissue loss at 12 months. Deficits also spread posteriorly over time into the occipital cortex on the medial wall. The significance maps (Figs 3, 5) all refer to the results of point-wise 2-tailed paired \( t \)-tests in each treatment group, comparing the average profile of gray matter between baseline and each subsequent time point. Frontal regions showed the greatest deficits, although these were not prominent at 3 months and became intense only at the 6- and 12-month follow-up. Relative to the baseline scans, there was already evidence for progressive gray matter loss at 3 months (L hem.: \( P < 0.032 \), R hem.: \( P < 0.0048 \)), and at 6 months (L hem.: \( P < 0.018 \), R hem.: \( P < 0.0076 \)), and at 12 months (L hem.: \( P < 0.024 \), R hem.: \( P < 0.0094 \); permutation tests). These changes were significant even after the appropriate multiple comparisons correction for surveying the whole cortex (\( P \) values above are all corrected). These tests all refer to significant changes from baseline within treatment groups; Figure 7 and Section 3.4, below, present treatment differences in these baseline-to-endpoint changes.

Trajectory of Gray Matter Deficits with OLZ Treatment

In OLZ-treated patients, regions of significant progressive gray matter loss were found at all time points, but these were less intense and widespread. These changes also evolved in a distinct anatomical trajectory; see Figure 5 and the time-lapse video maps at http://www.loni.ucla.edu/~thompson/MOVIES/HGDH/sz.html. Diffuse medial wall regions showed progressive gray matter volume deficits, as did restricted regions of the superior central and precentral gyri and precuneus—areas in which progressive loss was most prominent in a previous 5-year study of childhood-onset schizophrenia.
Examination of the individual subjects’ data also confirmed that this was not attributable to a processing artifact. Cingulate and paracingulate areas showed no detectable deficits at any time point, but progressive tissue loss occurred in right medial parietal and left medial prefrontal areas. Relative to baseline, progressive deficits were found at 3 months (L hem.: $P < 0.0086$, R hem.: $P < 0.0024$), and at 6 months (L hem.: $P < 0.034$, R hem.: $P < 0.036$), and at 12 months (L hem.: $P < 0.0088$, R hem.: $P < 0.004$; permutation tests). Again, these progressive changes were significant even after multiple comparisons correction for surveying the whole cortex. Changes occurred more posteriorly in the OLZ group, with changes in posterior (including occipital) and limbic regions, suggesting that the treatment is not entirely protective, as these changes are regionally much higher than would be predicted to occur normally, based on large cross-sectional studies of healthy subjects (Sowell et al. 2003; $N = 176$ subjects, aged 7–87).

**Average Rates of Gray Matter Changes**

Figure 6 shows the average gray matter loss rate, over each time interval, based on comparing each follow-up scan to the baseline scan and computing a rate-of-change map for each treatment group. To better understand how the loss rates change over time, the total change, as a percent of baseline, was divided by the time that had elapsed between scans (in years), giving an average loss rate for each interval (we did not assume that the changes proceed linearly with time, nor that they continue after the first year at the same rate; more frequent scanning would be needed to tell whether a disproportionate amount of the changes occur earlier or later in the interval).

Consistent with the significance maps for progression (Figs 3, 5), the HAL group showed gray matter changes at annualized rates of up to 10% per year in the first 3 months (Fig. 6), consistent with the highest loss rates in earlier studies (Thompson et al. 2001; Vidal et al. 2006). By 6 months after psychosis onset, the regions with greatest loss rates in the HAL group had shifted anteriorly into lateral and medial frontal and prefrontal cortices (Fig. 6). If rates were computed from the baseline and 1-year scans only, a lower time-averaged loss rate of 5% per year would be inferred for the most affected regions, in a predominantly frontal pattern (Fig. 6). In the OLZ group, mean loss rates were not significantly different from zero for most cortical regions at 3 months. Limited progressive loss occurred in superior central/postcentral sensorimotor gyri, a region that did not overlap with areas of progression on HAL.
Childhood-onset patients in our prior study showed a comparable pattern of superior cortical reduction over a 5-year period (Thompson et al. 2001). Figure 5 suggests that for both treatment groups (more for HAL than for OLZ), the pattern of loss spreads as time progresses. Figure 6 also shows that rates of loss attenuate after 6 months, based on computing rates of change at each time point with respect to baseline. At 3 months and 6 months, the patterns in both figures (Fig. 5: total loss and Fig. 6: loss rates) show correspondence, but the 12-month maps are completely different (as can be seen from comparing row 3 in Fig. 5 with row 5 in Fig. 6). Taken together, this strongly suggests that the rate of gray matter loss, in the HAL group, is highly nonlinear, in that the total loss (Fig. 5) is severe by 12 months, but the loss rate has normalized by 12 months (Fig. 6).

In fact, if the loss rate on both treatments were annualized (incorrectly assuming a linear rate of loss) over the full 12-month interval, the differences between treatments are less pronounced. This emphasizes the need to avoid assuming the trajectory is linear. As such, we stress that we report annualized loss rates in Figure 6 in percent per year, but these rates are not constant throughout that year, so we show maps separately for the 3-, 6-, and 12-month intervals.

Longitudinal Scans after 12 Months

Given that the clinical trial on which this analysis was based involved extensive MR imaging at multiple time points, the attrition rate for patients was quite high. Although scans were collected at 24 months from a subset of the patients examined here, the power for a statistical analysis of changes beyond 12 months was severely limited as only 5 HAL-treated patients and 16 OLZ-treated patients had scans at the 24-month point as well as all 4 earlier time points (0, 3, 6, 12 months). Even so, for the subjects with available data, in each group, we compared the 12- and 24-month values for whole-brain gray matter volume, frontal lobe volume, frontal cortical gray matter, and temporal cortical gray matter (combining lobar data from left and right hemispheres, and computing measures as in Lieberman et al. 2005). We restricted our analyses to the set of patients from whom we had made cortical maps in this study. All childhood-onset patients in our prior study showed a comparable pattern of superior cortical reduction over a 5-year period (Thompson et al. 2001).

Figure 5. Time-dependent trajectory of gray matter loss differs in HAL- versus OLZ-treated groups. Maps show cortical regions with significant gray matter loss (red), relative to the baseline scans, for each treatment group, at 3, 6, and 12 months after psychosis onset. Frontal deficits intensify in the HAL group, but are most prominent only after the 12-month period by which time greatest symptom normalization has occurred (see Fig. 8). The OLZ group shows subtler progressive deficits in the precuneus but not in the frontal cortices.
measures showed no further significant changes between 12 and 24 months, with the exception of the temporal lobe cortical gray matter, which fell in the OLZ group from $150.5 \pm 25.0$ SD cc at 12-months to $135.4 \pm 34.1$ cc at 24-months ($N = 16; P = 0.038$, 1-tailed). This result should be considered cautiously given the lack of significance in the 4 measures assessed for change in 2 groups. Even so, data from the prior study of a larger sample (Lieberman et al. 2005) suggested that the 12- and 24-month measures for whole-brain and lobar tissue volumes were comparable, suggesting either that 1) progressive brain changes are not readily detected beyond 12 months, and/or that 2) sample attrition over time in a clinical trial setting makes it difficult to compile a sample with enough subjects and statistical power to detect changes beyond 12 months.

**Differences between Treatments**

Figure 7 shows regions in which the HAL group showed less gray matter (i.e., greater tissue deficits) than the OLZ group at each time point (there are no significant differences between treatment groups at baseline as patients were randomized to each treatment). As expected from the progression patterns (Fig. 5), treatment differences were significant in lateral prefrontal and medial wall regions. Three and 6-month follow-up scans show greater deficits in the HAL group, which reach significance in the left hemisphere ($P < 0.018$ at 3 months, $P < 0.041$ at 6 months) but not on the right. The differences between the treatment arms were no longer significant by 12 months. We conducted a *post hoc* test to see if differences could be detected with a very crude single numeric measure of average gray matter density across the whole cortex. This measure was lower in the HAL group at 6 months ($P < 0.040$), but there were no group differences at baseline, 3 or 12 months (all $P > 0.1$). The topography of treatment differences is somewhat consistent across hemispheres and time points, but as it requires the detection of very small percentage differences in mean progression rates, it is a weak effect compared with the overall effects of progression in each group.

**Correlation between Gray Matter Deficits and Symptom Normalization**

Given the interest in correlating treatment efficacy with gray matter volumes or loss rates, we assessed these correlations...
using statistical maps (given the range of clinical measures assessed, the mapping analyses should be regarded as exploratory only). Total PANSS scores fell significantly over time, denoting clinical improvement, for both the HAL ($P < 6.8 \times 10^{-3}$) and OLZ ($P < 2.3 \times 10^{-5}$) groups, between baseline and 3-month scans (Fig. 8); most of the improvement occurred in the first 3 months (as in McGlashan et al. 2006). Both treatments were associated with improvements in subscale measures of negative symptoms, positive symptoms, and general psychopathology ($P = 0.05$ at 3-, 6-, and 12-month time points, except for negative symptoms at 3-months for OLZ, where $P = 0.1$). Mean clinical scores were no different between treatment groups at any time point (all $P > 0.05$), and symptom normalization was comparable for both groups (Fig. 8). We also correlated gray matter density with each PANSS subscale, and total PANSS scores. Some cortical regions showed voxel-level correlations with behavioral measures (e.g., negative symptoms at 6 months; $P = 0.053$, corrected, when groups were pooled; $P = 0.014$, corrected, for negative symptoms, in the HAL group, and $P = 0.04$, corrected for total PANSS scores at 6 months in the HAL group), but these effects were not significant after correcting for the 4 test scores for which correlations were performed. No correlations were found with QLS (Heinrichs et al. 1984) at 3 and 12 months, although these also improved over the 3- to 12-month time interval (from mean values of 79.1 to 86.8 in the OLZ group and from 71.3 to 88.2 in the HAL group; $P = 0.008$ for an increase; no treatment difference). We also correlated gray matter changes with measures of cognitive improvement, focusing on the cognitive assessments that showed differential treatment effects in Keefe et al. (2004). This study found that the Continuous Performance Test (Identical Pairs $d'$ score) improved more in the OLZ than the HAL group, when 0- and 12-week scores were

Figure 7. Differences between treatments. Brain regions are shown where HAL-treated subjects have greater gray matter deficits than OLZ-treated subjects. At 3 and 6 months after baseline, medial and superior cortical gray matter regions show greater deficits in the HAL group. By 12 months after psychosis onset, the only region where HAL shows greater deficits is in the frontal cortex, and this treatment difference is not significant after stringent multiple comparisons correction. Corrected $P$ values are shown for each hemisphere at each time point. The lower values, shown in parentheses, are for post hoc tests in which the smoothing kernel radius was optimized (a parameter in the definition of gray matter density).
compared; as a post hoc exploratory test we hypothesized that this difference may be associated with differences in gray matter maps or in estimated rates of change at 12 weeks. Even so, neither the absolute scores on this task, nor the degree of improvement, correlated with the gray matter density at 12 weeks or with changes in gray matter density between 12 weeks and baseline. The OLZ group gained more body weight than the HAL group (on average 17.0 ± 9.3 kg vs. 6.3 ± 4.9 kg; P = 0.0002 for a treatment difference), but neither the amount of weight gained nor absolute body weight linked with gray matter maps at any time point. Linkages may be detectable in larger subject samples, but our gray matter maps did not correlate with clinical or cognitive outcome measures at any time point, in groups pooled or analyzed separately. Despite significant treatment differences in one hemisphere at the first 2 time points, at the end of the year, no differences were found, there were no significant correlations with clinical measures.

**Medication Dose and Loss**

In each medication group, we correlated medication dose and cortical loss at each time point, and did not find any significant effects (see Fig. 9 for maps). To be as thorough as possible, we performed separate correlations with the mean dose over the 12 months of the study, and also with the final dose that the patient was taking at the time of the 12-month scan. Figure 9 shows example maps of the significance of correlations between cortical loss and the mean dose over the 12 months of the study, in each treatment arm. Mean doses were 4.827 ± 3.616 SD for the HAL group, and 10.297 ± 2.600 for the OLZ group. As there was a relatively small range in doses, the power of the correlation test may be limited by the limited range of doses used. The mean doses at each time point in the study are shown in Figure 10.

**Discussion**

In this paper, we have shown that OLZ and HAL differ in terms of their association with the trajectory of gray matter change in schizophrenia. The mechanisms for this difference may include altered neurotoxic or enhanced neuroprotective effects, among other interpretations. Whether this association reflects either reduced neurotoxicity or neuroprotection cannot be addressed by imaging data collected from living patients, and...
we emphasize that it remains speculative at this point. In
addition, it is possible that the volume changes relate to glial
and not neural components, as suggested by studies of these
same 2 medications in monkeys’ brain (Selemon et al. 1999;
Wang et al. 2004).

These trajectories of schizophrenia progression, visualized
here for the first time for different treatments, are remarkable
for 3 reasons. First, patients treated with HAL exhibited
a parietal-to-frontal wave of gray matter loss, intensifying in
scans acquired 3 and 6 months after their first psychotic
episode, but attenuating by 12 months. In our adolescent-onset
study, cortical deficits also spread anteriorly in the brain over
a 5-year period (Thompson et al. 2001). The trajectory is
essentially the opposite to the neurodegenerative pattern in
Alzheimer’s disease, where cortical degeneration spreads from
the medial temporal lobe entorhinal cortex in a forward wave
through the limbic system, consistent with the spread of
neurofibrillary tangles and amyloid pathology (Thompson et al.
2004). Atrophic rates in Alzheimer’s Disease are also roughly
twice as fast as the fastest changes seen here. Frontal deficits
worsened in prior longitudinal studies of schizophrenia that did
not distinguish between patients receiving different neuro-
leptics (Ho et al. 2003), and are consistent with the extensive
literature on frontal lobe dysfunction in first-episode, at-risk,
and prodromal subjects (Cannon et al. 2003; Narr et al. 2005;
Vidal et al. 2006). The second surprising finding of this study is
that OLZ-treated patients showed significant progressive gray
matter reductions, but in a more restricted anatomical pattern
than in HAL-treated patients. Third, symptom measures did not
correlate with the extent or rate of gray matter reduction. This
may be due to lack of power, as our prior assessment of the full
sample (Lieberman et al. 2003) \((N = 161)\) showed that 1) in
HAL-treated patients, less improvement in neurocognitive
functioning was associated with greater decrease in gray
matter volumes; and 2) in OLZ-treated patients, greater
improvements in PANSS total and negative scores were
associated with less lateral ventricular volume increase.

Symptoms were reduced in both treatment groups (Fig. 7),
and functional recovery—whose primary cause is neurorecep-
tor blockade—might be causally disconnected from the
ongoing deterioration in brain structure, so long as patients
remain on medication. If patients were to go off medication,
symptoms may be unmasked with a severity related to the
underlying structural deficit. Cahn et al. (2006) found that
increased gray matter loss in the first year predicted both
a higher positive and negative symptom score \((P = 0.03\) and \(P =

Figure 9. Medication dose and loss. These maps show the significance of any
correlation between medication dose and cortical gray matter density at the 12-
month time point, within the HAL-treated group (top panel) and the OLZ-treated
group (bottom panel). The effects are not significant after multiple comparisons
correction. Similar (nonsignificant) maps were obtained when correlating cortical loss
with the mean drug dose used over the first 12 months of the study. As the range of
doses used was fairly consistent across patients, the power to detect a dose effect
was very limited, and the study was not designed to assess a dose effect. Even so,
variations in dosing did not explain variations within the treatment arms.

Figure 10. Mean drug dose for each randomized treatment group. Here the mean dose is shown for the HAL- and OLZ-treated groups, at 0, 3, 6, and 12 months after initial treatment.
0.002, respectively) and a decreased likelihood of living independently ($P = 0.001$) when patients were examined 5 years later. Sometimes, mapping techniques may offer statistical advantages over volumetry in detecting correlations between clinical measures and anatomical differences that are either distributed or do not coincide well with any anatomical partition that is known a priori. Even so, in this report it did not help perform point-wise correlations with cognition as still no significant correlations with clinical measures were found.

Our childhood-onset study mapped a dynamic wave of gray matter loss, which spread from parietal-to-frontal cortices over a 5-year period (Thompson et al. 2001; Vidal et al. 2006). Early-onset schizophrenia is neurobiologically continuous with the adult-onset disorder, but typically has a more severe course and poorer outcomes. The spreading wave was considered to represent the disease process interacting with normal brain development (Pantelis et al. 2003), but here we also found a strikingly similar trajectory in adult-onset patients receiving HAL, despite these subjects being a decade older. As many developmental processes continue until middle age (Bartzokis et al. 2003), late intracortical myelination processes that continue throughout life may be derailed in schizophrenia (Peters and Sethares 2004). Alternatively, these gray matter volume deficits may reflect an active disease process that occurs early in the illness. Whether psychosis onset occurs in adolescence or adulthood, active pathophysiology may be combined with exaggerated or dysregulated neurodevelopment (Woods 1998; Lieberman 1999; Lieberman et al. 2001). These structural differences are extremely dynamic in the first year after psychosis onset; this serves as a caveat to researchers seeking an MRI-based biological marker for genetic or diagnostically discriminative purposes (Woods et al. 2001), suggesting that the deficit level varies substantially over time and with treatment.

The typical parietal-to-frontal disease trajectory was not present in OLZ-treated patients although some posterior cortical changes occurred—this is consistent with the only other voxel-based MRI study that compared typical and atypical antipsychotics in schizophrenia. In this study, Dazzan et al. (2005) compared first-episode patients cross-sectionally 8 weeks after first treatment. Their study was neither longitudinal (Woods 1998; Lieberman 1999; Lieberman et al. 2001). These structural differences are extremely dynamic in the first year after psychosis onset, this serves as a caveat to researchers seeking an MRI-based biological marker for genetic or diagnostic purposes (Woods et al. 2001), suggesting that the deficit level varies substantially over time and with treatment.

The cortical effects they reported are highly consistent with the patterns seen here after 3 months (Fig. 5), and may have different mechanisms than the subcortical gray matter changes. The basal ganglia becomes hypertrophied when patients are treated with typical, but not atypical, neuroleptics (Buchsbaum et al. 1987; Bartlett et al. 1994; Chakos et al. 1995; Holcomb et al. 1996; Heitmiller et al. 2004), and this volume excess reverses after change in treatment to clozapine, an atypical neuroleptic (Chakos et al. 1995). Cell processes may “sprout” or synaptogenesis may occur (Konradi and Hecker 2001) specifically in the striatum where DR-D2 receptors are most densely concentrated, and may not account for the cortical changes. More likely, the cortical effect may be due to a glial response. In primates treated with atypical neuroleptics, prefrontal glial cells proliferate, leading to cortical hypertrophy, which may functionally deter any destructive process (Selemon et al. 1999). OLZ stimulates glial cell division in the frontal cortex of adult rats (Wang et al. 2004), and this may promote some form of neuroprotection, via correction of impaired myelination (Bartzokis et al. 2003; Ho et al. 2003; Hof et al. 2003), and metabolic support against abnormally severe dendritic pruning and/or neurotoxic ablation of synapses. Even so, most studies do not find that neuroleptics increase neurogenesis, so the mechanism of the observed changes is not clear.

In this study, differences between the treatment arms were no longer significant by 12 months, suggesting that whatever the difference between the treatments is, the difference may be in the timing of the changes, rather than having a different anatomical trajectory. Although the HAL changes occur early, it cannot be ruled out that the OLZ group may “catch up” given enough time; further analyses of the available longitudinal scans after the 12 month time point would be useful to clarify this, although the substantial attrition of subjects in this trial makes it difficult to make inferences based on the very few scans available at all 5 time points including 2 years. Long-term studies are vital to determine whether the treatment difference is an issue of timing or if there is a real difference in the anatomical selectivity of gray matter reduction.

HAL treatment may be neurotoxic (Goff et al. 1995; Wright et al. 1998; Molina 2005), which may account for some of the observable gray matter attrition. Macaque monkeys, treated for 17–27 months with high doses of HAL or OLZ (Dorph-Petersen et al. 2005), showed a slight, but significant, brain volume decrease for both medications, with greatest reductions in frontal and parietal regions (a pattern seen here in the HAL maps, and in Lieberman et al. 2005). In humans treated with typical antipsychotics, frontal gray matter reduction is correlated with the dose (Gur et al. 1998), and chronic HAL, but not OLZ, administration induces oxidative damage in the rat brain (Reinke et al. 2004). Even so, in most human histological studies, neuronal loss is not detectable in patients treated with HAL for decades (Harrison and Lewis 2003). Medication-free prodromal subjects exhibit accelerated frontal tissue reduction relative to controls (Pantelis et al. 2003), suggesting that the loss process is not attributable solely to medication.

OLZ may ameliorate the pathophysiological effects that cause disease progression and gray matter volume reductions in schizophrenia. In preclinical studies, clozapine and OLZ antagonize the effects of glutamate (Duncan et al. 2000), 6-OH-dopamine lesioning (Wang et al. 2004), oxidative stress (Wang et al. 2004), and can stimulate the synthesis of trophic molecules (Chlan-Fournier et al. 2002; Marx et al. 2003; Parikh et al. 2004; Wang et al. 2004) and even neurogenesis (Wang et al. 2004). These results suggest that there are pharmacologic mechanisms that go beyond symptom suppression via neuroreceptor antagonism and ameliorate the underlying pathophysiology that causes disease progression and the clinical deterioration that is the hallmark of the illness. Consistent with this, symptom normalization lags behind the dopamine and serotonin receptor blockade that occurs within hours of antipsychotic treatment (as confirmed with receptor-based positron emission tomography; Kapur and Seeman 2000).

OLZ may affect brain lipids and myelination. In childhood-onset patients scanned longitudinally, white matter growth rates were silenced relative to controls (Gogtay et al. forthcoming). In adult patients, white matter volume does not increase as in healthy controls (Bartzokis et al. 2003; Ho et al. 2003) and its integrity may be compromised (Szeszko et al. 2005; Kubicki et al. 2004; Wang et al. 2004) and even neurogenesis (Wang et al. 2004). These results suggest that there are pharmacologic mechanisms that go beyond symptom suppression via neuroreceptor antagonism and ameliorate the underlying pathophysiology that causes disease progression and the clinical deterioration that is the hallmark of the illness. Consistent with this, symptom normalization lags behind the dopamine and serotonin receptor blockade that occurs within hours of antipsychotic treatment (as confirmed with receptor-based positron emission tomography; Kapur and Seeman 2000).
A psychosis-related disruption in intracortical myelination may contribute to changes in cortical morphology (Hartzokis et al. 2003). Some antipsychotics may positively affect the balance between myelin production and decline, perhaps by inducing oligodendrocyte proliferation and compensating for oligodendrocyte reductions (Ho et al. 2003). Such a response, as well as associated intracellular neuronal changes, may help to ameliorate psychotic symptoms.

Magnitude of Brain Changes
Any maps, such as those in Figure 6, that suggest annualized rates of gray matter that reach 10% in small, restricted anatomical regions on HAL must be reconciled with prior MR and post-mortem studies showing that patients with schizophrenia have no more than a loss of about 3% of their gray matter compared with controls—in total. There are several possible reasons for this discrepancy. The first is that if the profile of deficits is not spatially homogeneous, in any spatially detailed map of atrophic rates, there will be some regions with greater average loss rates than would be reflected by a spatial average over a larger region that contains that area. This can be seen in the HAL maps at the 12 month time point (Fig. 6)—even though the annualized loss rate is as high as 6% in some regions, it is near zero in the central gyrus and frontal poles. If these regions were included in an overall frontal lobe region-of-interest, the apparent loss for the overall region would be much lower, around the 3% that is consistent with the pathological literature. A second hypothesis, which may or may not be plausible, is that if the region of greatest loss rate is truly small and shifts anatomically, then the total loss for the whole brain may be much less than that seen at specific locations in the maps of loss rates, as the focus of loss is shifting. Given the pathological literature, it is plausible that an annualized loss of around 3% per year persists beyond the first year. In fact, our maps tend to point to the opposite conclusion, that much of the loss on HAL has already occurred by 6 months after initial treatment. In childhood-onset schizophrenia (COS), where greater loss is reported than in adults, longitudinal studies suggest that the rate of cortical loss seen in COS during adolescence plateaus during early adulthood (Arango and Kahn 2008).

Nonlinearity of Progressive Brain Changes
It is clear from the comparisons of each time point to baseline that the changes over time are not linear. In fact, we were reluctant to adopt a specific linear or nonlinear model for the trajectory over time, as it was conceivable that all changes might occur in the acute interval very soon after initial treatment (i.e., T1 to T2). As such, we did not choose to fit the effect of time using a linear or nonlinear regression through all 4 scans (using time as an explanatory variable), but instead we performed a direct t-test comparing each time point with baseline (which does not invoke any specific model of how the change occurs between the time points). As such, we are not using the model of linear regression in our analysis, we are just comparing time points in pairs. In addition, to assess group effects, we performed a group comparison at each time point (which is not affected by choices in modeling the effect of time as a continuous function).

Sample Composition
This study included subjects who had diagnoses of schizophrenia, schizoaffective disorder, and bipolar disorder according to DSM-IV criteria (as assessed with the Structured Clinical Interview for DSM-IV, Research Version). As such, this heterogeneity may have influenced measures made at baseline and may be relevant to the potential effects of drug treatment. Patients with schizophrenia and schizoaffective disorder are typically combined in antipsychotic treatment trials (e.g., Kane et al. 2002), and there is a continuing debate on whether schizoaffective disorder represents a diagnostic entity that can be biologically distinguished from schizophrenia (Kempf et al. 2005). No studies, to our knowledge, have directly compared gray matter distribution between patients with schizoaffective disorder and schizophrenia, but studies of bipolar disorder without psychosis have shown significantly decreased cortical thickness in frontal and limbic areas (Lyoo et al. 2006); lithium treatment also appears to have a trophic effect on gray matter (Bearden et al. 2007). In a longitudinal comparison of schizoaffective disorder, schizophrenia, and mood disorder with and without psychosis, Harrow et al. (2000) found that the patients with mood disorder without psychosis had the best prognosis, whereas those with schizophrenia had the worst. The patients with mood disorder with psychosis and schizoaffective disorder had progressively worsening intermediate courses, suggesting a progressive course comparable to that in schizophrenia. Further study is required to determine whether patients with schizoaffective disorder have a trajectory that is distinguishable from that of the overall groups examined here.

Differences after 1 Year
A key limitation of this study is that, given the apparent intensification of the disease process, there were no differences between the treatment arms at 12 months. In that context it cannot be said that the medication alters the final pattern of brain structure at the end of the study. It may be that the trajectory of loss in time is initially drug-dependent and then significant losses have accumulated in both groups by the time they have received substantial medication. Again, we note that the technique and numbers are only sensitive to general effects between groups, and the paths for specific individuals may vary from these mean trajectories.

Limitations
This study has several additional limitations. First, we did not map brain changes in a normal healthy reference population at the same ages and intervals, which may have shed light on whether normally occurring changes were intensified in either treatment group. Strictly speaking, this study did have a control group, in the sense that 2 randomized treatments were being compared, but ethical considerations prevented the treatment of normal subjects with either medication, or the use of a placebo in the patients. As such, without an absolute control condition it is difficult to be sure that the effect is either due to toxic effects of one drug versus protective effects of another (among other interpretations) and it cannot be determined what the normal trajectory of such change is in schizophrenia. Even so, even a placebo design were ethical, it would not truly distinguish medication effects from disease effects in schizophrenia, as they clearly interact and medication effects may not be distinguishable as a logically separate process, even in principle. In addition, our past studies mapping cortical change in large cohorts of healthy subjects over the lifespan (Sowell et al. 2003; N = 176 subjects aged 7–87) show that changes are very subtle in normals during early adulthood, and would be
extremely difficult to detect in subjects followed up with MRI after only 3, 6, and 12 months. Detecting brain changes with MRI over short follow-up intervals is the topic of significant efforts in scanner calibration and image postprocessing (Leow et al. 2006), as it would shorten the minimum follow-up interval in a drug trial.

A second caveat is needed regarding the interpretation of gray matter changes on MRI. Gray matter density, studied here, is a surrogate measure of disease progression, and links with clinical decline and duration of illness in Alzheimer’s disease, epilepsy, and HIV/AIDS (Thompson et al. 2004, 2005; Lin et al. 2006). Density is a derived measure, which depends, among other things, on applied smoothing, and does not represent regional volume, although it does correlate highly with cortical thickness (Narr et al. 2006). Some caveats are therefore needed in relating any MRI structural intensity measure to presumed cellular losses in gray matter. Although there is no widely accepted cellular substrate of schizophrenia, dynamic maps such as these are valuable for generating hypotheses, especially given the shifting nature of the observed changes.

A third caveat pertains to the statistical inference used with brain maps. The permutation methods here provide an overall significance level for multiple comparisons in the maps as a whole. Here we preferred to survey the whole brain without constraining the search region, but permutation testing can be restricted to frontal or temporal regions of interest to provide better localizing power and to increase statistical power by excluding some brain regions with no hypothesized effects (as we have done in prior studies). Strictly speaking, if that were the case only observations used in those regions of interest should be used for inference in the study, so we preferred a more conservative approach that sacrificed some inferential power but avoided the potential bias of testing only brain regions that were implicated in past studies. An additional caveat was that we assessed longitudinal changes within each group, and between group differences at each time point. Because of the large numbers of multiple comparisons and the small cohort (144 scans including patients with all 4 scans), we did not have sufficient power to detect a significant group by time interaction, or a group by region by time interaction, as this would strengthen the findings of a differential change in the 2 groups.

The cortical pattern matching approach has mapped the trajectory of disease in many studies, and increases statistical power by adjusting for intersubject variation in cortical features, and localizing deficits relative to sulcal landmarks. Even so, the maps are more time-consuming to create than whole-brain or lobar volume measures—these remain the same as we have done in prior studies. Strictly speaking, if that were the case only observations used in those regions of interest should be used for inference in the study, so we preferred a more conservative approach that sacrificed some inferential power but avoided the potential bias of testing only brain regions that were implicated in past studies. An additional caveat was that we assessed longitudinal changes within each group, and between group differences at each time point. Because of the large numbers of multiple comparisons and the small cohort (144 scans including patients with all 4 scans), we did not have sufficient power to detect a significant group by time interaction, or a group by region by time interaction, as this would strengthen the findings of a differential change in the 2 groups.

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Notes
HGDH Study Group: HGDH is a naming code used by the sponsor and has no significance. HGDH Study Group members participated in the design of the study and are listed in Lieberman et al. (2005). Authors P.T., G.B., A.T., C.C., D.P., J.M., R.H., M.T., G.T., J.L. designed the study; all authors performed the research, analyzed the data, and contributed to writing the paper. Conflict of Interest: None declared.

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