Magnetic Resonance Imaging Predictors of Treatment Response in First-Episode Schizophrenia

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Identifying neurobiological predictors of response to antipsychotics in patients with schizophrenia is a critical goal of translational psychiatry. Few studies, however, have investigated the relationship between indices of brain structure and treatment response in the context of a controlled clinical trial. In this study, we sought to identify magnetic resonance (MR) imaging measures of the brain that predict treatment response in patients experiencing a first-episode of schizophrenia. Structural MR imaging scans were acquired in 39 patients experiencing a first-episode of schizophrenia with minimal or no prior exposure to antipsychotics participating in a double-blind 16-week clinical trial comparing the efficacy of risperidone vs olanzapine. Twenty-five patients were classified as responders by meeting operationally defined treatment response criteria on 2 consecutive study visits. Fourteen patients never responded to antipsychotic medication at any point during the clinical trial. MR imaging scans were also acquired in 45 age- and sex-matched healthy volunteers. Cortical pattern matching methods were used to compare cortical thickness and asymmetry measures among groups. Statistical mapping results, confirmed by permutation testing, indicated that responders had greater cortical thickness in occipital regions and greater frontal cortical asymmetry compared with nonresponders. Moreover, among responders, greater thickness in temporal regions was associated with less time to respond. Our findings are consistent with the hypothesis that plasticity and cortical thickness may be more preserved in responders and that MR imaging may assist in the prediction of antipsychotic drug response in patients experiencing a first-episode of schizophrenia.

Key words: schizophrenia/treatment response/MR imaging/gray matter/asymmetry

Introduction

In patients experiencing a first-episode of schizophrenia, pharmacological intervention may be challenging, and there can be considerable heterogeneity in how patients respond to antipsychotic treatment. An important goal of translational psychiatry is the identification of predictors of treatment response given that these measures may inform intervention to potentially alter the course of illness. Understanding the relationship between brain structure and treatment response in schizophrenia has particular relevance for translational approaches given that antipsychotic treatment may be associated with changes in brain volume. Moreover, key brain regions, including the prefrontal cortex, which have been hypothesized to play a role in abnormal information processing in schizophrenia, appear to be strongly influenced by atypical antipsychotics through their D2 and 5HT properties. Magnetic resonance (MR) imaging may be particularly suited for providing quantitative in vivo measures of the brain in translational psychiatry studies given its noninvasive nature, relative ease of acquisition, and widespread availability.

Several studies reported that MR imaging morphometry could be utilized to predict treatment response and functional outcome in patients with schizophrenia. Moreover, changes in white matter volume were identified in patients who responded to antipsychotic...
medications, and differences in white matter integrity, as inferred from diffusion tensor imaging, have been used to predict treatment response in schizophrenia with some success. Possible limitations with prior studies investigating the relationship between MR imaging measures of the brain and treatment response/outcome include the use of patients with extensive prior exposure to antipsychotic medications and the lack of controlled treatment trials from which to predict strictly defined response criteria. Although conventional volumetric measures have been used to predict response with some success, the use of cortical surface mapping algorithms has been largely unexplored in this context. Such methods can control for interindividual differences in anatomy and allow highly localized changes in gray matter thickness or other morphometric characteristics such as hemispheric shape asymmetries to be compared between groups.

The goal of this study was to identify MR imaging predictors of treatment response in patients experiencing a first-episode of schizophrenia using cortical pattern matching to quantify gray matter thickness and cortical asymmetry. Based on prior work suggesting that cortical gray matter deficits predicted antipsychotic dose escalation and that antipsychotic response was associated with larger brain volume, we predicted that greater gray matter thickness would be associated with response to antipsychotic medications. In addition, based on our prior work indicating that abnormal cerebral “torque” was associated with worse functional outcome in schizophrenia, we further predicted that greater hemispheric shape asymmetry would be associated with antipsychotic response. Patients were studied early in the course of illness and either psychotropic drug-naive or with minimal prior exposure to minimize potential confounds associated with prior pharmacotherapy.

Methods

Subjects

The 39 patients included in this study were recruited from admissions to the inpatient service at The Zucker Hillside Hospital in Glen Oaks, NY, and were participating in a National Institute of Mental Health–funded randomized 16-week clinical trial comparing the efficacy of olanzapine vs risperidone. Further details regarding the overall clinical trial have been published elsewhere. In addition, patients have participated in our prior studies investigating cortical thickness and asymmetry in schizophrenia compared with healthy volunteers. All patients were interviewed using the Structured Clinical Interview for Axis I Disorders and Schizophrenia Change Version with psychosis and disorganization items: severity of delusions, severity of hallucinations, impaired understandability, derailment, illogical thinking, bizarre behavior, and a rating of “much” or “very much” improved on the Clinical Global Improvement scale. Date of treatment response was defined as the date of the first of the 2 consecutive study visits meeting improvement criteria. Intraclass correlation coefficients among 3 raters for the items comprising the positive symptom response criteria were as follows: severity of delusions = 0.79, severity of hallucinations = 0.90, impaired

Antipsychotic Titration Schedule And Response Criteria

The initial daily dose for patients in the treatment trial was 2.5 mg for olanzapine and 1 mg for risperidone. After 1 week, dose increases occurred at intervals of 1–3 weeks until the subject improved or reached a maximum daily dose of 20 mg of olanzapine or 6 mg of risperidone. Lorazepam was prescribed for agitation. Subjects with persistent mood symptoms unresponsive to antipsychotic treatment were prescribed sertraline for depression or divalproex sodium for manic symptoms. For the present study, treatment response was operationally defined using criteria described previously and included meeting all the following criteria on 2 consecutive study visits—a rating of 3 or less on the following Schedule for Affective Disorders and Schizophrenia Change Version with psychosis and disorganization items: severity of delusions, severity of hallucinations, impaired understandability, derailment, illogical thinking, bizarre behavior, and a rating of “much” or “very much” improved on the Clinical Global Improvement scale. Date of treatment response was defined as the date of the first of the 2 consecutive study visits meeting improvement criteria. Intraclass correlation coefficients among 3 raters for the items comprising the positive symptom response criteria were as follows: severity of delusions = 0.79, severity of hallucinations = 0.90, impaired
understandability = 0.66, derailment = 0.67, illogical thinking = 0.82, and bizarre behavior = 0.97. The intraclass correlation for the Clinical Global Improvement severity score was .63.

Based on the response criteria, 25 patients were classified as responders and 14 patients were classified as nonresponders. Responders responded, on average, following 7.8 (SD = 3.9) weeks of treatment in the clinical trial. Among patients classified as nonresponders, we only included individuals who completed the full 16-week clinical trial and did not respond to study medication at any point during the trial. Seven nonresponders and 12 responders received olanzapine at study entry, whereas 7 nonresponders and 13 responders received risperidone at study entry.

Patient Medication History

Of the 25 responders, 15 were antipsychotic drug naive at the time of the MR imaging exam. Two responders received their MR imaging exam prior to the initiation of antipsychotic treatment in the clinical trial. The remaining 8 responders had received, on average, 5.0 (SD = 3.2) days of treatment in the clinical trial at the time of the MR imaging exam. Of the 14 nonresponders, 5 were antipsychotic drug naive at the time of the MR imaging exam. Four nonresponders received their MR imaging exam prior to the initiation of antipsychotic treatment in the clinical trial. The remaining 5 nonresponders had received, on average, 7.6 (SD = 4.4) days of treatment in the clinical trial at the time of the MR imaging exam.

Handedness

Classification of handedness was based on a modified version of the Edinburgh Inventory consisting of 20 items. Total number of right- and left-hand items was scored, and the laterality quotient was computed according to the following formula: (Total R – Total L)/(Total R + Total L). This yielded a total laterality quotient for each subject that ranged from +1.00 (totally dextral) to −1.00 (totally nondextral). Subjects with a laterality quotient greater than .70 were classified as dextral and the rest as nondextral. Handedness for 1 patient and 1 healthy volunteer was based on preference for handwriting alone.

Image Acquisition And Preprocessing

MR imaging exams were conducted at the Long Island Jewish Medical Center and were acquired in the coronal plane using a 3D Fast SPGR sequence with IR Prep on a 1.5-T whole-body superconducting imaging system (General Electric, Milwaukee, Wisconsin). This sequence produced 124 contiguous images (slice thickness = 1.5 mm) through the whole head with in-plane resolution of .86 × .86 mm² in a 256 × 256 matrix. Image processing included a series of functions performed on the T₁-weighted images similar to those described previously and included (1) whole-brain extraction to remove non–brain tissue and the cerebellum; (2) correction for inhomogeneities; (3) correction for head tilt and alignment using a 3-translation and 3-rotation rigid-body transformation; (4) transformation of MR images into a common stereotaxic space without scaling; (5) automated tissue classification using a partial volume classifier method where voxels are labeled as most representative of white matter, gray matter, or cerebral spinal fluid (CSF); and (6) surface rendering to produce 3D object models representative of the shape of the cortex. For surface rendering, a spherical mesh surface was deformed to fit a cortical surface tissue threshold intensity value (a signal value that differentiates extra cortical CSF and brain tissue) from the brain volume rigidly aligned in ICBM-305 space. Finally, 29 sulcal landmarks were delineated manually in each hemisphere using validated protocols and previously published reliability procedures.

Cortical Thickness Analysis

Previously detailed cortical pattern matching methods were used to spatially relate homologous regions of cortex between subjects to permit measurement and comparison of cortical thickness at homologous hemispheric locations among individuals. Briefly, for matching of anatomy, manually identified sulcal and gyral landmarks were used as anchors to drive the surrounding cortical surface anatomy of each individual into correspondence. These warping algorithms, which serve to relate corresponding sulcal and gyral regions without scaling, allow cortical thickness measurements to be made at each of 65 536 spatially associated cortical surface points in each hemisphere. Using an implementation of the 3D Eikonal equation, cortical thickness was defined as the shortest 3D distance, without crossing voxels classified as CSF, from the cortical white-gray matter boundary to the hemispheric surface (gray matter-CSF boundary). Subsequently, cortical thickness values sampled at high spatial density in each subject were compared between groups as described below. It should be noted that the correlation between cortical thickness averaged across the brain and total gray matter volume was $r = .285$ ($P < .008$) in the current dataset. Thus, although a portion of the variance overlaps, these measures appear to reflect different attributes of brain structure, and it is reasonable that regional changes in cortical thickness may be present even in the absence of differences in whole-brain gray matter volume as has been shown in prior studies of clinical populations.

Asymmetry Index Analysis

Cortical pattern matching methods were also used as the basis for estimating cerebral asymmetry. Specifically, to identify regional changes in shape between the hemispheres, a distance measure was first computed from...
the anterior commissure point at midline (defined as the origin) to each spatially matched location on the hemispheric surface. These distance measures thus reflect variations in hemispheric radial width/length, where, for instance, individuals showing typical right-frontal and left-occipital protrusions would exhibit larger distance measures in the respective hemispheric region. An asymmetry index \((L - R) / [0.5 \times (L + R)]\) was then computed from measures reflecting the distance from the origin for each subject. These asymmetry indices again sampled at high spatial density were used for the subsequent comparison of hemispheric shape asymmetries among groups.

**Statistical Analyses**

To examine regional thickness differences, statistical comparisons were made at each of the cortical surface locations in 3D space using the statistical program R (www.r-project.org) to reveal regionally specific cortical thickness changes across the cortex between groups using the general linear model. These results were then mapped onto the 3D group–averaged hemispheric surface models, where statistically significant results were indexed in color. Comparisons of cortical thickness among healthy volunteers, responders, and nonresponders included age, sex, and total intracranial contents as statistical covariates. Additional covariates involving the comparison of responders with nonresponders included study medication and cumulative exposure to antipsychotics at the time of the MR imaging exam. Additional analyses were performed to examine the relationship between time to response and cortical thickness and asymmetry measures among the group of responders \((N = 25)\) using Pearson’s product moment correlations with total intracranial contents, study medication, and cumulative exposure to antipsychotics as statistical covariates. For group analyses investigating gray matter thickness and cortical asymmetry, we used an uncorrected 2-tailed alpha level of \(P < .05\) as the threshold for statistical significance. Because measurements were compared at thousands of spatially correlated locations, we confirmed significant findings by performing permutation analyses \((N = 10 000; P < .05, 2\text{ tailed})\) within regions-of-interest defined by the LONI Probabilistic Brain Atlas. An illustration of these regions is provided in figure 1. We excluded the caudate, hippocampus, insular cortex, and putamen from analysis because these regions do not have areas that connect with the outer cortex as well as the brainstem and cerebellum.

**Results**

There were no significant differences in distributions of age, sex, handedness, race, total gray matter, total white matter, or total CSF volumes among healthy volunteers, responders, or nonresponders (table 1). In addition, responders did not differ from nonresponders in the number of antipsychotic drug-naïve patients, days of antipsychotic exposure at the time of the MR imaging exam, number of patients with either a substance abuse or a dependence diagnosis, and baseline ratings from the global

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**Fig. 1.** An Illustration of the Regions-of-Interest Defined by the LPBA40 Atlas Used in the Current Study.
The 16-week survival estimates for sustained response among the 39 patients with MR imaging were 63.2% (±22%) for olanzapine and 65.0% (±21%) for risperidone; the two 95% CIs at 16 weeks were essentially the same. Mean (SD) end-of-study dosage for olanzapine was 9.0 mg (SD = 4.8) for responders and 15.2 mg (SD = 3.9) for nonresponders. Mean end-of-study dosage for risperidone was 3.8 mg (SD = 1.2) for responders and 5.0 mg (1.1) for nonresponders. At the Zucker Hillside Hospital site, there were no significant differences in age, sex, age at first psychotic symptoms, handedness, and education between patients with MR imaging exams who participated in the current study compared with patients from the clinical trial not included in the present study.

Both responders and nonresponders had relatively widespread thinning across the cortical surface compared with healthy volunteers with effects most pronounced in posterior cingulate, ventral prefrontal, and posterior temporal/occipital regions (figures 2A and B). Notably, there was a relative absence of areas showing greater cortical thickness in patient groups with respect to controls. For the comparison of responders vs healthy volunteers, uncorrected findings illustrated in the statistical maps survived permutation testing for the following left hemisphere regions: angular gyrus, fusiform gyrus, inferior frontal gyrus, inferior temporal gyrus, postcentral gyrus, precentral gyrus, precentral gyrus, precuneus, superior temporal gyrus, and supramarginal gyrus. In the comparison of nonresponders vs healthy volunteers, the right middle orbitofrontal region survived permutation testing. Compared with responders, nonresponders had significant cortical thinning in the occipital and prefrontal regions (figure 2C). Results of permutation testing confirmed the presence of regional cortical thinning in nonresponders compared with responders. We also investigated the relationship between time to respond and cortical thickness among patients who responded to antipsychotic medications, where uncorrected results are shown in figure 3. Permutation testing indicated that time to respond was correlated significantly with gray matter thickness in the right and left inferior temporal gyri. Specifically, less time to

### Table 1. Sample Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Nonresponders</th>
<th>Responders</th>
<th>Healthy Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (y)</strong></td>
<td>25.6 (5.9)</td>
<td>23.0 (4.1)</td>
<td>24.8 (6.5)</td>
</tr>
<tr>
<td><strong>Sex (M/F)</strong></td>
<td>12/2</td>
<td>18/7</td>
<td>29/16</td>
</tr>
<tr>
<td><strong>Handedness (R/L)</strong></td>
<td>10/4</td>
<td>20/5</td>
<td>31/9</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td>7, 5, 0, 2, 0</td>
<td>6, 10, 4, 3, 2</td>
<td>24, 9, 6, 4, 2</td>
</tr>
<tr>
<td><strong>Brain volumes (cm³)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gray matter</td>
<td>608 (47)</td>
<td>632 (68)</td>
<td>636 (64)</td>
</tr>
<tr>
<td>White matter</td>
<td>424 (48)</td>
<td>436 (73)</td>
<td>425 (51)</td>
</tr>
<tr>
<td>CSF</td>
<td>145 (17)</td>
<td>146 (27)</td>
<td>141 (24)</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD, unless otherwise indicated. CSF, cerebral spinal fluid; M/F, male/female; R/L, right/left. *Handedness data were missing for 5 healthy control subjects. Race coded as Caucasian, African American, Hispanic, Asian, Other. Due to the low number of expected frequencies in some categories of race, the latter 3 groups (ie, Hispanic, Asian and Other) were combined into a single group for analysis.

Fig. 2. Significant (P < .05, Uncorrected) Differences in Cortical Thickness Encoded in Color in Responders Compared With Healthy Volunteers (Panel A), Nonresponders Compared With Healthy Volunteers (Panel B), And Responders Compared With Nonresponders (Panel C).
respond to antipsychotics was associated with greater thickness in these regions.

Significant differences in hemispheric shape asymmetries among groups are illustrated in figures 4A–C. Compared with healthy volunteers, responders demonstrated abnormalities in cortical asymmetry that were most evident in inferior temporal and occipital regions (figure 4A). Results of permutation testing confirmed significant effects in the fusiform gyrus and inferior temporal gyrus. In contrast, compared with healthy volunteers, nonresponders demonstrated abnormalities in cortical asymmetry that were most pronounced in frontal regions (figure 4B) with effects in the inferior frontal, middle frontal, and lateral orbitofrontal gyri surviving permutation testing. A direct comparison of responders and nonresponders revealed a lack of frontal asymmetry among nonresponders (figure 4C) with significant effects observed in the middle frontal gyrus following permutation testing. In addition, average hemispheric shape asymmetries mapped on the averaged left hemisphere within each group are illustrated in figure 5. These maps converge with the group comparisons to indicate that nonresponders have a lack of hemispheric asymmetry, which was most pronounced in frontal regions.

Fig. 3. Significant Correlations Between Time to Response And Cortical Thickness Among The Responders (N = 25). Note: Hot colors denote negative correlations and cool colors denote positive correlations.

Fig. 4. Significant Differences (Uncorrected P values Encoded in Color) in Asymmetry Indices Encoded in Color in Responders Compared With Healthy Volunteers (Panel A), Nonresponders Compared With Healthy Volunteers (Panel B), and Responders Compared with Nonresponders (Panel C).
Our findings suggest that quantitative MR imaging measures can be used to predict response to antipsychotic medications in patients experiencing a first-episode of schizophrenia. Specifically, patients who did not respond to atypical antipsychotics had less occipital gray matter thickness as well as prefrontal cortical thickness deficits compared with patients who responded to treatment. Moreover, nonresponders demonstrated an abnormal pattern of frontal cortical asymmetry compared with both responders and healthy volunteers. Strengths of the current study include the use of cortical pattern matching methods that may increase sensitivity for detecting regional changes in cortical thickness and hemispheric asymmetry and the use of patients with minimal or no prior antipsychotic drug exposure. In addition, we used stringent response criteria that were operationally defined in the context of a controlled treatment trial. In particular, the criterion for outcome should be high in patients experiencing a first-episode of schizophrenia, and in this study, patients were considered to be responders only following significant sustained improvement. Early neuroimaging studies suggested that ventricular enlargement was associated with worse outcome and poor response in patients with schizophrenia. More recently, several studies investigated morphometric measures in relationship to treatment response in schizophrenia, but findings have been mixed. In several studies, patients with schizophrenia with brain atrophy benefited from olanzapine and responded clinically to alprazolam augmentation. Similarly, Zipursky et al reported that cortical gray matter deficit predicted the need for dose escalation due to poor clinical response. In contrast, other work indicates that patients who responded to antipsychotics had larger hippocampal and frontal volumes compared with patients who did not respond and that partially responsive patients with larger brain volumes may be more likely to experience the benefits of clozapine treatment. Our data converge with prior studies suggesting that patients with schizophrenia most likely to derive clinical benefit from antipsychotic medications have greater gray matter thickness compared with nonresponders and healthy volunteers.

Our findings further suggest that in patients with schizophrenia, antipsychotic response is associated with occipital cortex thickness. This region, while less widely implicated in the pathophysiology of schizophrenia compared with frontal and temporal lobe regions, has been hypothesized to play a critical role in mediating visual processing deficits that have been identified in patients as well as their unaffected first-degree relatives. In particular, abnormalities in the magnocellular pathway have been hypothesized to contribute to higher-level visual cognitive deficits in patients. Disturbances in visual attention circuitry have been reported during a visual oddball paradigm, and visual evoked potential abnormalities were identified in occipital regions. In addition, Butler et al reported that patients with schizophrenia demonstrated white matter abnormalities, as assessed...
via diffusion tensor imaging, in the optic radiations. Hyperactivation was also observed among individuals at high risk for psychosis in the lingual, fusiform, and middle occipital gyri regions while performing an emotion discrimination task.\textsuperscript{32}

Several lines of research support the finding that occipital lobe gray matter thickness is associated with treatment response in schizophrenia. For example, Molina et al\textsuperscript{33} reported that clozapine treatment was associated with increased occipital metabolism, including primary and association visual cortex, and additionally, that changes in positive symptoms correlated with increased activity in visual regions. In addition, Ramos et al\textsuperscript{34} reported that treatment-resistant patients with schizophrenia had abnormal electroencephalographic (EEG) patterns in the occipital region. The purported mechanism through which the occipital gray matter could play a role in treatment response was not addressed in the present study, but animal data indicate that administration of antipsychotics is associated with D2 upregulation in all the major brain lobules, including the occipital lobe\textsuperscript{35} as well as an increase in nerve growth factor in the occipital cortex.\textsuperscript{36} Moreover, lower levels of neurotensin-like immunoreactivity were observed in the occipital cortex following risperidone administration,\textsuperscript{37} and changes in EEG patterns were observed in occipital regions between the first and second week after haloperidol depot injection.\textsuperscript{38} These studies as well as the current findings thus converge to support a role for the occipital region in mediating effective antipsychotic treatment response.

Our study also provides evidence that frontal cortical asymmetry was associated with antipsychotic treatment response. Cortical asymmetry abnormalities in schizophrenia have been reported across a wide range of studies including those investigating EEG,\textsuperscript{39} event-related potential,\textsuperscript{40} and symptom\textsuperscript{41} measures. Abnormalities in cerebral asymmetry, especially in language regions, have been one of the most robust findings in patients with schizophrenia.\textsuperscript{42} Moreover, cortical thickness asymmetry measures have been used to distinguish healthy controls from patients with first-episode schizophrenia and individuals at risk for psychosis.\textsuperscript{43} There are limited data, however, linking asymmetry deficits to treatment response or outcome. Thus, in this regard, it may be noteworthy that we reported previously that patients with schizophrenia did not demonstrate the normal pattern of cerebral asymmetry evident in healthy volunteers\textsuperscript{44} and that more normal cerebral asymmetry was associated with adequate social/vocational functioning and full recovery in patients.\textsuperscript{12} Moreover, Falkai et al\textsuperscript{45} reported that patients with schizophrenia who were antipsychotic nonresponders demonstrated a significant reduction in frontal lobe asymmetry as assessed using computerized tomography. It is conceivable that a disruption in normal brain asymmetry, which likely forms in utero,\textsuperscript{46,47} could be associated with abnormal patterns of right-left hemisphere dopamine neurotransmission observed in striatal brain regions, which have been hypothesized to mediate antipsychotic drug response, in patients with schizophrenia.\textsuperscript{48}

Greater gray matter thickness in both right and left temporal lobe regions was associated with a faster time to respond to antipsychotic medications in the subgroup of patients who responded. Temporal lobe regions have been critically implicated in the pathophysiology of schizophrenia\textsuperscript{49,50} with some evidence that gray matter loss is associated with the transition to psychosis,\textsuperscript{51} but the structural integrity of this region in mediating faster response to antipsychotic medications has not been well investigated. Our findings are consistent, however, with Molina and colleagues,\textsuperscript{52} who reported that positive symptom improvement was associated with temporal lobe gray matter volume among treatment resistant patients receiving clozapine. Similarly, Woods et al\textsuperscript{53} noted treatment-associated changes in temporal lobe regions among patients with schizophrenia-spectrum diagnoses using MR spectroscopy. Moreover, treatment with haloperidol, remoxipride, or clozapine was associated with D1 receptor downregulation in prefrontal and temporal lobe regions, suggesting that they may be important for therapeutic response to antipsychotics in schizophrenia.\textsuperscript{35}

There were a number of study limitations that should be acknowledged. The sample of nonresponders was small, and thus, there is the possibility that this may have contributed to low statistical power resulting in a type II error. For example, the uncorrected statistical maps showed prefrontal cortical thinning in nonresponders compared with responders, but some of these effects did not survive permutation testing possibly because variance was greater and effect sizes were smaller. There is also the increased likelihood of a type I error given the large number of statistical tests performed, although we tried to minimize this possibility through the use of permutation testing. Nonresponders tended to be older than responders, although we included age as a statistical covariate in the analyses. In addition, our study did not have the statistical power to investigate the possible differential effects of the 2 study drugs in relationship to the brain imaging measures. An additional caveat is that our findings may not be generalizable to patients from the clinical trial who did not want to have an MR imaging exam or dropped out of the study prematurely due to noncompliance.

In sum, our findings suggest that MR imaging may be used to identify a subgroup of patients who do not respond to atypical antipsychotic medications early in the course of illness. This possibility could be tested further by examining cortical thickness and hemispheric shape asymmetry measures in treatment-resistant patients, including those receiving clozapine. In addition, better understanding the relationship between these
structural MR imaging indices and measures of brain function would be an important goal of future studies.

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