Original Investigation

Cortical Folding Defects as Markers of Poor Treatment Response in First-Episode Psychosis

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IMPORTANCE At present, no reliable predictors exist to distinguish future responders from nonresponders to treatment during the first episode of psychosis. Among potential neuroimaging predictors of treatment response, gyrification represents an important marker of the integrity of normal cortical development that may characterize, already at illness onset, a subgroup of patients with particularly poor outcome.

OBJECTIVE To determine whether patients with first-episode psychosis who do not respond to 12 weeks of antipsychotic treatment already have significant gyrification defects at illness onset.

DESIGN Case-control study with 12 weeks' longitudinal follow-up to determine treatment response.

SETTING Secondary psychiatric services in an inner-city area (South London, England).

PARTICIPANTS A total of 126 subjects, including 80 patients presenting with first-episode psychosis and 46 healthy controls. Patients were scanned at the outset and received various antipsychotic medications in a naturalistic clinical setting. They were followed up for 12 weeks and classified as responders or nonresponders if they reached criteria for symptom remission, evaluated with the Psychiatric and Personal History Schedule.

OBSERVATION Patients were exposed to naturalistic antipsychotic treatment for 12 weeks following a magnetic resonance imaging scan.

MAIN OUTCOMES AND MEASURES Cortical gyrification was assessed using local gyrification index in a vertexwise fashion across the entire cortical surface with correction for multiple testing using permutation analysis. Differences in local gyrification index were assessed between responders, nonresponders, and healthy controls. The effect of diagnosis (affective vs nonaffective psychosis) on the local gyrification index was also investigated in responders and nonresponders.

RESULTS Patients with first-episode psychosis showed a significant reduction in gyrification (hypogyria) across multiple brain regions compared with healthy controls. Interestingly, nonresponders showed prominent hypogyria at bilateral insular, left frontal, and right temporal regions when compared with responders (all clusters significant at $P < .05$). These effects were present for both affective and nonaffective psychoses.

CONCLUSIONS AND RELEVANCE Gyrification appears to be a useful predictor of antipsychotic treatment response. Early neurodevelopmental aberrations may predict unfavorable prognosis in psychosis, irrespective of the existing diagnostic boundaries.

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At present, there is no reliable predictor of treatment response in first-episode psychosis (FEP). Early treatment response is thought to be one of the strongest predictors of subsequent functional outcome in psychosis[1,2]; also, early responders are less likely to experience further psychotic episodes following illness onset.[3] The potential of neuroimaging studies to provide measures of translational importance in predicting treatment response and reducing the duration of psychotic episodes has become paramount.[4] Hence, it is essential to ascertain high-yield neuroimaging measures with a predictive potential by studying their association with prospective treatment response.

Several neuroimaging studies have investigated the relationship between treatment response and brain structure in psychosis. However, a pooled analysis of these studies showed no significant relationship between brain morphology and treatment response, possibly because of significant heterogeneity in illness duration, duration of untreated psychosis (DUP), age, and duration of treatment of the subject groups included in the analyses.[5] More recent studies have found some support for the notion that diminished gray matter tissue in patients with psychosis is associated with poor treatment response.[6-8] We have previously shown that structural magnetic resonance imaging (MRI) can indeed contribute to personalized predictions of longitudinal outcome in FEP,[4] although discrepancies exist in the localization and the direction of the changes.[9] These inconsistencies are in part due to the varying levels of prior exposure to antipsychotics across studies[7,9] and the use of voxel-based morphometry (VBM), a method that measures gray matter density or volume, which can be confounded by the presence of altered surface morphology.[10,11] Importantly, the presence of abnormal sulcal patterning in schizophrenia, putatively linked to aberrant neurodevelopment,[10] increases the likelihood of observing inconsistent results when using template-based registration for VBM. Recent methodological advances in structural imaging have allowed us to study the surface anatomy in greater detail.[12] Such surface-based approaches have been used successfully to study clinically important variables in psychosis, such as the risk of transition to overt psychosis from the prodromal state,[13] the effects of antipsychotic treatment,[14] and the persistence of symptom burden despite treatment.[15]

Among various anatomical measures that can be studied using structural MRI, cortical gyrification holds a distinct potential to investigate early neurodevelopmental disturbances that may contribute to the pathophysiology of psychosis[12,16] and that may characterize, already at illness onset, a subgroup of patients with particularly poor outcome.[17,18] Defects in gyrification have been associated with exposure to obstetric complications, known to contribute to an elevated risk of schizophrenia.[19-21] Cortical gyrification has also been observed to be a structural marker of later neurodevelopmental outcome in preterm infants.[22] Furthermore, and relevant to this study, regional abnormalities in gyrification seem associated with the expression of core psychotic symptoms that persist despite treatment.[23,24] Also, given the proposed differences in the degree of neurodevelopmental aberrations in affective and nonaffective psychosis,[25] the study of gyrification could po-

tentially aid in predicting diagnostic differences in psychosis. Interestingly, early neuroimaging studies investigating the structural correlates of treatment response have observed an inverse relationship between prefrontal sulcal width and treatment response to clozapine in schizophrenia.[26-28] Although this indicates an association between folding patterns and treatment response, these studies were methodologically limited by the use of 2-dimensional computed tomography–based measurements from manual drawings on preselected brain regions and by the evaluation of subjects with prolonged exposure to antipsychotics. To date, no MRI study has explored the relationship between the local gyrification pattern across the entire cortex and subsequent treatment response in FEP with minimal antipsychotic exposure.

In this study, we investigated the gyrification pattern across the entire cortical surface using a vertexwise mapping approach in patients with FEP, grouped on the basis of their subsequent response to treatment at 12 weeks. Given evidence that reduced gray matter is associated with poor treatment response,[6-8] we predicted that, already at illness onset, nonresponders would show widespread abnormalities in gyrification when compared with responders or healthy controls. Further, given evidence of differences in the degree of neurodevelopmental abnormalities in affective and nonaffective psychosis,[25] we also performed an exploratory investigation of diagnostic differences in gyrification and evaluated the effect of diagnosis on the relationship between gyrification and treatment response.

Methods

Participants

Patients with FEP were recruited from the South London and Maudsley National Health Service Foundation Trust, South East London, England. We defined FEP as the first-ever presentation to secondary psychiatric services with evidence of any of the following: delusions, hallucinations, thought disorder, or negative symptoms of schizophrenia, which would be scored 4 or higher on the Positive and Negative Syndrome Scale (PANSS) and had lasted for at least 7 days (Nottingham Onset Schedule[29]). All patients with a functional psychotic illness (International Statistical Classification of Diseases, 10th Revision [ICD-10] codes F10-19, excluding coding F1x.0 for acute intoxication; F20-29 and F30-39, psychosis codes) were invited to participate. A sample of healthy controls similar to the patient group in age, sex, ethnicity, educational qualifications, and employment status was recruited from the same geographical area. Controls were administered the Psychosis Screening Questionnaire,[30] and they were excluded if they reported any psychotic symptom or had a history of any psychotic illness.

Exclusion criteria for all subjects were the following: history of head trauma or injury with loss of consciousness lasting longer than 1 hour; history of any serious medical or surgical illness; learning disabilities; current or past organic psychosis; lack of English fluency; and known contraindications to conventional MRI. A posteriori exclusion criteria (af-

ter neuroimaging acquisition) included any evidence of neuroradiological abnormality or problems with scan acquisition and motion artifacts. Ethical permission was obtained from the South London and Maudsley National Health Service Foundation Trust and Institute of Psychiatry research ethics committee. After complete description of the study to the subjects, written informed consent was obtained. A total of 80 patients and 46 healthy controls were included in this study.

Clinical Assessment

Diagnosis was made using the Operational Criteria system[31] according to *ICD-10* criteria, using patient clinical notes for the month after their first contact with psychiatric services. All diagnoses were performed by qualified psychiatrists, subject to comprehensive training and achievement of good interrater reliability (κ = 0.91). Patients diagnosed as having bipolar disorder or major depression with psychotic symptoms were included in the affective psychosis group, while patients with schizophrenia, schizophreniform disorder, schizoaffective disorder, and psychosis not otherwise specified formed the nonaffective psychosis group.

Severity of psychotic symptoms was evaluated on the day of MRI and then again after 12 weeks using the PANSS.[32] The DUP was quantified as the interval between first onset of psychotic symptoms and first contact with psychiatric services, using information from medical records, patient interview, and significant others. The duration of illness was defined as including both the DUP and the time between contact with services and the MRI scan (time of treated illness). Because of their relevance to neuroimaging studies,[33] detailed information on dose of antipsychotic drugs and duration of exposure to them was collected during face-to-face interviews, from clinical notes, and from interviews with the clinical team. Antipsychotic doses were converted to chlorpromazine equivalents, according to defined criteria,[34,35] to estimate the total daily chlorpromazine-equivalent dose, calculated by summing all daily doses from the first day of treatment with antipsychotics up to the day of MRI. The majority of the patients (n = 62) were taking atypical antipsychotics (35 olanzapine, 18 risperidone, 4 quetiapine fumarate, and 5 aripiprazole), 3 were taking typical antipsychotics (1 each were receiving haloperidol, amisulpride, and flupenthixol), and 15 were medication naive. Premorbid IQ was assessed using the New Adult Reading Test.[36] Handedness was assessed according to the Annett Hand Preference Questionnaire.[37]

Evaluation of Treatment Response

We evaluated response to treatment 12 weeks after MRI because of the clinical recommendation that antipsychotic treatment with a specific drug should be continued for 6 to 8 weeks before switching to a different medication owing to lack of efficacy or to adverse effects.[38] Hence, we considered that a 12-week interval would provide information on treatment response following at least 1 drug taken for an appropriate period (even by allowing for delay in starting or optimizing the medication regimen).

Response to treatment was our primary outcome measure and was evaluated using information obtained from clinical records, patient face-to-face interviews, and reports from informants using the World Health Organization Personal and Psychiatric History Schedule, a standardized instrument to record symptoms' presence and severity that has been successfully used in World Health Organization multicenter studies of the incidence and outcome of schizophrenia.[39] Response was operationalized as a reduction in symptom severity to the levels required by the remission criteria of the Schizophrenia Working Group Consensus.[40] This consensus established a set of criteria that provide an absolute threshold in severity of symptoms that should be reached for clinical improvement. This approach was therefore preferred to symptom change cutoffs for this naturalistic study. In fact, cutoff points are often arbitrary, affected by variability in baseline symptom severity across studies, and are not understood intuitively by clinicians.[40,41] Instead, the remission criteria proposed by the consensus are more suited for traditional concepts of remission in psychiatric disorders.[40] According to these criteria, clinical improvement is reached when a simultaneous rating of mild or less (equivalent to 1, 2, or 3) is given in the following items of the PANSS: delusions (P1), unusual thought content (G9), hallucinatory behavior (P3), conceptual organization (P2), mannerisms/posturing (G5), blunted affect (N1), social withdrawal (N4), and lack of spontaneity (N6). To this end, we considered the Personal and Psychiatric History Schedule scores equivalent to the PANSS scores as follows: 0 was equivalent to PANSS scores 1, 2, and 3; 1 was equivalent to PANSS scores 5 and 6; and 2 was equivalent to PANSS scores 7 and 8. Using this method, 40 patients were classified as responders and 40 as nonresponders.

MRI Acquisition and Processing

The MRI scans were obtained as soon as possible after first contact with the psychiatric services, whenever deemed appropriate by the treating clinician, to ensure minimal exposure to antipsychotic medications in patients. All MRI scans were acquired in a 3-T Signa HDx scanner (General Electric) at the Centre for Neuroimaging Sciences, Institute of Psychiatry, London, England. A sagittal 3-dimensional magnetization-prepared rapid-acquisition gradient-echo volumetric scan was obtained from each subject. The scan had an image matrix size of 256 × 256 × 166 voxels, with an in-plane voxel size of 1.02 × 1.02 mm and a slice thickness of 1.2 mm (echo time, 2.848 milliseconds; repetition time, 6.988 milliseconds; inversion time, 650 milliseconds; excitation flip angle, 20°; 1 data average). Full brain and skull coverage was required for the MRI data sets, and detailed quality control was carried out on all MRIs according to previously published quality control criteria.[42]

Cortical Gyrification Analysis

Surface extraction was completed using FreeSurfer version 4.5.0 software.[43] The preprocessing was performed according to the standard description given by Fischl et al.[44] Briefly, following skull-stripping and intensity correction, the gray matter–white matter boundary for each cortical hemisphere was determined using tissue intensity and neighborhood constraints. The resulting surface boundary was tessellated to gen-

erate multiple vertices across the whole brain before inflating. The expansion of the gray matter–white matter boundary created the pial surface with a point to point correspondence. This was followed by spherical morphing and spherical registration using sulcogyral landmarks. Local gyrification indices (LGIs) were obtained using the method of Schaer et al[45] in line with previous studies.[11,23,46] The method by Schaer and colleagues is an automated vertexwise extension of the Zilles gyrification index, which computes a ratio of the inner folded contour to the outer perimeter of the cortex[47] using images reconstructed through the FreeSurfer pipeline.[48] It provides an LGI for each of the thousands of vertices on the reconstructed cortical surface, which serves as a measure of the amount of cortex buried in the locality of each vertex. An LGI value of 1 assigned to a vertex suggests that the vertex is located on a flat pial surface with no sulcal ridges in its vicinity. We used a 25-mm spherical region of interest around each vertex to compute the LGI.

Statistical Analysis

Baseline clinical and demographic variables were compared using analysis of variance or χ^2 test. Log transformation was undertaken to ensure normality for variables with a skewed distribution. Between-group differences in cortical gyrification were estimated using the query-estimate-design-contrast interface in the FreeSurfer software. We used a general linear model controlling for the effects of age, sex, and intracranial volume to estimate differences in gyrification among responders, nonresponders, and healthy controls at each vertex of the right and left hemispheric surfaces. In addition, when comparing responders and nonresponders, we explored the effect of diagnosis (affective vs nonaffective psychosis) and the interaction between diagnosis and categorical treatment response. Furthermore, we studied the effect of diagnostic status in the 2 treatment groups (responders and nonresponders) independently, controlling for the effects of age, sex, and intracranial volume. The Monte-Carlo permutation approach implemented in the FreeSurfer software was used for statistical correction of multiple comparisons.[49] For the different clusters observed using a cluster-forming threshold of $P < .05$, we estimated the probability of observing a cluster of equal (or greater) spatial extent from the null distribution of data across 10 000 permutations. Clusterwise probability values of $P < .05$ were considered statistically significant.

Results

Clinical Variables

The clinical and demographic characteristics of the sample are shown in **Table 1**. There were no significant differences in the distribution of diagnostic categories between responders and nonresponders (proportion with nonaffective psychosis, 73% vs 68%, respectively; $\chi^2_1 = 0.24$; $P = .63$) (Table 1). There were no significant differences between responders and nonresponders in terms of handedness, total intracranial volumes, baseline PANSS negative scores, median DUP, median dura-

tion of illness, average dose or duration of antipsychotic treatment, or the proportion of antipsychotic-naive subjects at baseline (all $P > .05$) (Table 1) or in exposure to mood stabilizers, antidepressants, or benzodiazepines (data not shown). Responders had lower baseline total PANSS and positive PANSS scores than nonresponders. The patient group was slightly older than the healthy controls (mean [SD] age, 28.04 [8.0] vs 24.65 [5.63], respectively; $F = 6.39$; $P = .01$). Although there were no differences between groups in alcohol use, the healthy controls included a lower proportion of subjects with current or past use of other substances than either the responders or the nonresponders, which in contrast included similar proportions of users (51%, 75%, and 83%, respectively; $\chi^2_2 = 26.2$; $P < .001$).

Group Differences in Gyrification

All Patients vs Controls

When all patients with FEP were compared with the healthy controls, significant reductions in gyrification were observed in the middle/inferior frontal gyrus, precentral gyrus, and precuneus in the left hemisphere and the middle frontal gyrus and inferior parietal (angular gyrus) region in the right hemisphere (**Table 2** and eFigure 1 in Supplement). There were no regions with increased gyrification in patients.

Responders vs Nonresponders

Nonresponders showed reduced cortical folding (hypogyric regions) in several regions across the cortical surface when compared with responders, with no regions of increased folding (hypergyria). The hypogyria was predominantly observed in the insula, superior frontal, and rostral middle frontal regions in the left hemisphere and the inferior and superior temporal cortex extending to the insula and the temporal pole in the right hemisphere (**Figure** and Table 2).

Responders and Nonresponders vs Healthy Controls

Nonresponders showed reduced gyrification (hypogyric regions) in several brain regions when compared with healthy controls, including the bilateral middle frontal gyrus (extending to the precentral gyrus), the superior/inferior temporal cortex, angular gyrus, and medial occipital cortex on the right, and the posterior cingulate and precuneus extending to the medial occipital cortex on the left. Both responders and nonresponders showed significant hypogyria of the left lingual gyrus when compared with controls (Figure and Table 2). Responders had no other regional differences when compared with controls.

Given the baseline difference in total PANSS scores between responders and nonresponders, we repeated the analysis first including the total PANSS score and then the positive PANSS scores as covariates, and the results remained unaltered. Furthermore, vertexwise correlation analysis between the total PANSS score or the positive PANSS score and gyrification did not reveal any significant clusters of positive or negative correlations.

Gyrification in Affective and Nonaffective Psychosis

On the whole, patients with nonaffective psychosis showed several regions of reduced gyrification when compared with

Table 1. Clinical and Demographic Variables

Variable	Nonresponders (n = 40)	Responders (n = 40)	Healthy Controls (n = 46)	Statistic
Diagnosis, %				
Schizophrenia	64	55	...	
Schizoaffective disorder	8	8	...	
Bipolar disorder	10	18	...	$\chi^2 = 3.6$
Depressive disorder	15	13	...	
Other	3	5	...	
Psychosis, No.				
Affective	11	13	...	$\chi^2 = 0.24$
Nonaffective	29	27	...	
Age, mean (SD), y	28.1 (7.9)	28.0 (8.2)	24.7 (5.6)	$F = 3.17$[a]
Sex, No.				
Female	10	12	21	$\chi^2 = 4.5$
Male	30	28	25	
Education, mean (SD), y	13 (3.6)	13.4 (3.8)	14.7 (3.2)	$F = 2.1$[b]
IQ by NART, mean (SD)	93 (11)	90 (11)	95 (9)	$F = 2.0$[c]
Handedness, No.				
Left	2	3	7	$\chi^2 = 2.2$
Right	38	37	39	
Intracranial volume, mean (SD), cm³	1724 (212.8)	1753 (213.6)	1728 (189.4)	$F = 0.24$
Baseline PANSS score, mean (SD)				
Total	62.6 (13.4)	55.6 (12.5)	...	$F = 6.38$[a]
Positive	16.1 (6.7)	13.4 (4.6)	...	$F = 4.18$[a]
Negative	16.6 (6.3)	14.3 (5.8)	...	$F = 2.85$
Treatment duration at time of scan, mean (SD), d	38.0 (28.1)	42.6 (32.7)	...	$F = 0.43$
Treatment-naive subjects at time of scan, No.				
Affective	1	2	...	$\chi^2 = 0.08$
Nonaffective	6	6	...	
Dose at time of scan, mean (SD), chlorpromazine equivalents	244.9 (167.3)	223.1 (136.4)	...	$F = 0.34$
DUP, median (IQR), wk[b]	9 (3-74)	6 (1-24)	...	$Z = -1.52$
Time between contact with services and scan, median (IQR), wk	5 (2-8)	5 (3-10)	...	$Z = -0.41$
DOI at time of scan, median (IQR), wk[d]	18 (7-81)	13 (5-26)	...	$Z = -1.83$

Abbreviations: DOI, total duration of illness (both treated and untreated); DUP, duration of untreated psychosis; IQR, interquartile range; NART, National Adult Reading Test; PANSS, Positive and Negative Syndrome Scale; ellipses, not applicable.

[a] Group differences significant at $P < .05$.

[b] Based on 63 patients and 29 healthy controls.

[c] Based on 63 patients and 33 healthy controls.

[d] Mann-Whitney U tests.

those with affective psychosis (Table 2 and eFigure 1 in Supplement). There was no significant diagnosis × response interaction on gyrification. However, among nonresponders, there were no significant differences in gyrification between the 2 diagnostic groups. In contrast, among responders, patients with nonaffective psychosis had a significant reduction in the gyrification of bilateral insula including a portion of the Broca area as well as the medial orbitofrontal, dorsolateral prefrontal, and superior temporal sulci in the left hemisphere (eFigure 1 in Supplement).

Spatial Overlap Between the Effect of Diagnosis and Treatment Response

We created 2 binary masks, one including all significant clusters (thresholded at clusterwise significance of $P < .05$) from the analysis of responders vs nonresponders and the other including all significant clusters from the affective vs nonaffective psychosis comparison. We computed the proportion of spatial overlap (or intersection) between the 2 masks and derived

an inclusive mask that contained the vertices present in both masks (eFigure 2 in Supplement). Overall, this inclusive mask contained only 13.7% of all vertices that showed either an effect of diagnosis or treatment response, while 86.3% of vertices were nonoverlapping. The spatial overlap was noted in the bilateral insula, right anterior lateral prefrontal region, and right medial orbitofrontal region.

Discussion

In the first study, to our knowledge, using an unbiased whole-brain estimate of 3-dimensional gyrification to predict treatment response in FEP, we have shown that, already at illness onset, patients with FEP who subsequently do not respond to treatment have significant cortical folding defects compared with patients who subsequently respond and with healthy controls, while those who go on to respond are virtually indistinguishable from the controls. Furthermore, we have

Table 2. Group Differences in Gyrification Among Responders, Nonresponders, and Healthy Controls[a]

Cortical Region	Talairach Coordinates of Peak	Cluster Size, mm²	Clusterwise Probability, P Value
Healthy controls > all patients			
Left posterior cingulate/precuneus	−8, −40, 41	8304	<.001
Left precentral	−41, −12, 48	3589	<.001
Left middle/inferior frontal	−35, 36, 12	1167	.04
Right middle frontal cortex	33, 23, 43	1304	<.001
Right inferior parietal	45, −58, 36	755	.04
Responders > nonresponders			
Left insula/central sulcus	−57, −8, 10	3697	<.001
Right insula/lateral temporal	37, −13, 2	6703	<.001
Left superior frontal/midcingulate	−9, 32, 27	5080	<.001
Left middle frontal gyrus	−35, 51, −1	2581	<.001
Healthy controls > nonresponders			
Left posterior cingulate/precuneus	−9, −49, 26	7219	<.001
Left precentral	−37, 7, 37	3775	<.001
Right superior/middle frontal	20, 33, 34	3415	<.001
Right superior temporal	53, −30, 3	1811	<.001
Right cuneus/lingual gyrus	10, −58, 2	4382	<.001
Right insula/lateral temporal	37, −13, 2	4502	<.001
Left middle frontal	−38, 43, 5	2330	<.001
Right angular gyrus	45, −59, 36	1415	.002
Left inferior temporal	−53, −28, −24	792	.02
Left orbitofrontal	−33, 20, −17	1077	.003
Healthy controls > responders			
Left lingual	−4, −82, 1	862	.02
Nonaffective psychosis < affective psychosis			
Right insula/superior temporal	37, −12, 2	5778	<.001
Right inferior temporal	51, −27, −22	7245	<.001
Left insula/inferior frontal	−42, 19, 7	5870	<.001
Left middle frontal	−22, 44, 20	1037	.005
Right subgenual anterior cingulate	7, 15, −17	1245	<.001
Right posterior cingulate/precuneus	41, −81, 6	1809	<.001
Left lateral occipitotemporal	−49, −62, −2	4116	<.001
Left posterior cingulate	−4, −15, 31	1310	<.001

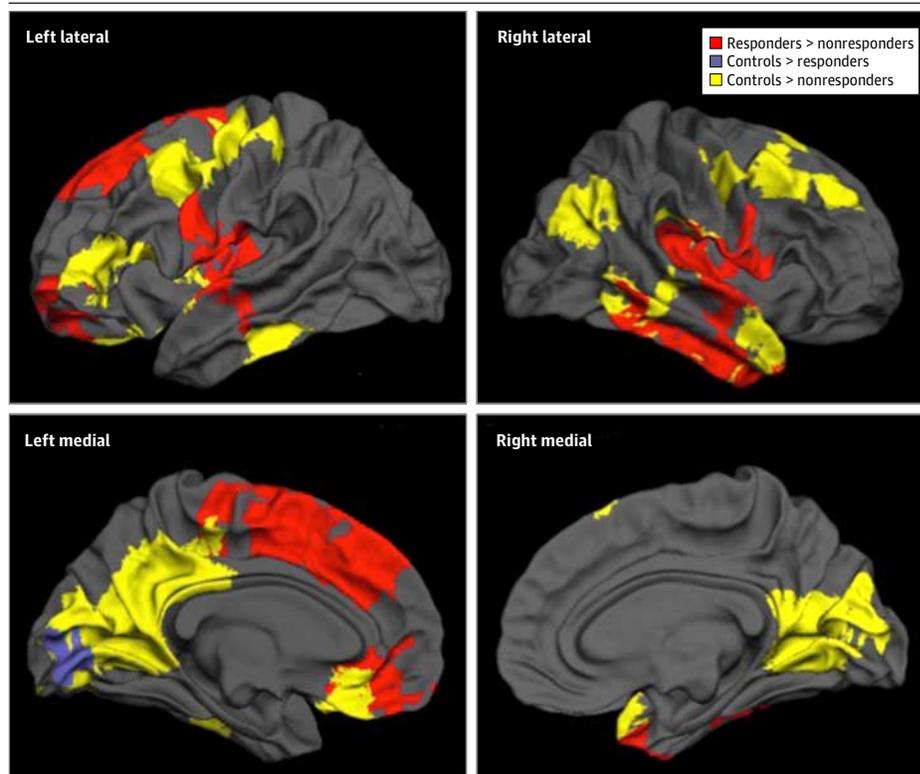[a] Threshold for inclusion in a cluster, $P < .05$.

shown that patients with nonaffective psychosis show a significant reduction in gyrification, in line with the notion of greater neurodevelopmental deficits in schizophrenia than affective psychosis.

Nonresponders had significant hypogyria of several frontotemporal regions and the insula when compared with responders, and they had more widespread deficits in gyrification extending to the precuneus, angular gyrus, and lingual gyrus when compared with healthy controls. Responders had notable hypogyria of the left lingual gyrus compared with healthy controls. These differences were not explained by the effects of age, sex, or diagnosis, although a small degree of overlap was noted between the spatial distribution of hypogyria related to treatment response and the hypogyria related to a diagnosis of nonaffective psychosis. The gyrification abnormalities that characterize poor treatment response in FEP seem largely distinct from the gyrification defects that characterize schizophrenia, but reduced insular, orbitofrontal, and lateral prefrontal gyrification may be shared by both schizophrenia and poor treatment response.

To our knowledge, no previous study has investigated the relationship between LGIs of the cortex and subsequent treatment response, making comparisons difficult. Although VBM and surface-based morphometric approaches are not directly comparable, our results may be interpreted as an extension of previous studies suggesting that diminished gray matter tissue in frontal and temporal cortex is associated with poor treatment response.[6-8,50] However, our finding of an inverse relationship between insular gyrification and treatment response is somewhat contrary to the finding by Molina et al[9] of a direct association between the degree of insular volume deficit estimated using a VBM approach and treatment response. Considering the inherent nature of VBM methods,[51] it is likely that patients with a differential insular folding may be classified as showing a reduction in the probabilistic gray matter volume. In fact, a significant portion of the variance in insular gray mat-

Figure. Clusters Showing Differences in Gyrification Among Responders, Nonresponders, and Controls

Left lateral

Right lateral

■ Responders > nonresponders
■ Controls > responders
■ Controls > nonresponders

Left medial

Right medial

No clusters showed significant results in the opposite directions to the contrasts shown in the Figure. All clusters are displayed on a reconstructed average white matter surface (fsaverage in FreeSurfer software) and survived multiple testing using Monte-Carlo simulation with a cluster inclusion criterion of P = .05. The left hemisphere is on the left side of the image, and the right hemisphere is on the right side. The exact values of clusterwise probability for the clusters are presented in Table 2.

ter measured using VBM in schizophrenia is not accounted for by surface anatomical measures such as thickness or surface area.[11] Nevertheless, our observation of prefrontal and insular hypogyria in association with nonresponse in FEP is consistent with previous observations of significant hypogyria in frontoinsular cortex in medicated patients with chronic schizophrenia and significant symptom burden despite clinical stability.[16] This consistency highlights the strength of using surface-based morphometry over other approaches to predict prognosis and treatment response.

Furthermore, various groups have linked the widening of sulcal width, which could lead to a hypogyric effect, to treatment response with clozapine in schizophrenia.[26-28] Unlike the inverse relationship observed with prefrontal sulcal width,[26-28] larger width of the perisylvian cerebrospinal fluid space (adjacent to the temporoinsular regions showing hypogyria in our study) has been associated with better response to clozapine,[52] suggesting that some structural indicators of poor response to early treatment can indeed predict better response to clozapine.

The insula is an integral part of a cognitive control/ salience network composed of anterior cingulate and connected to limbic subcortical structures, cerebellum, and dorsolateral prefrontal cortex.[53,54] This network has been proposed to play a cardinal role in the pathophysiology of psychosis.[55,56] Given our current observation of frontotemporoinsular hypogyria in nonresponders, other indices of abnormal cortical connectivity involving these structures might also help predict treatment response. Indeed, this has been previously shown

using functional MRI and cognitive behavioral therapy in medicated patients with schizophrenia.[57] Despite this apparent consistency, it is important to bear in mind that the integrity of other cortical/subcortical networks also contributes to treatment response.[58]

The comparison between the nonaffective and affective groups suggests that there is widespread hypogyria in patients with nonaffective psychosis. These changes were predominantly observed in regions with multimodal functions such as lateral prefrontal and lateral temporal regions, in addition to the paralimbic regions (insula, anterior cingulate, and posterior cingulate). This is coherent with conventional VBM studies showing less extensive gray matter reduction in first-episode bipolar disorder than in schizophrenia in comparison with healthy controls,[59-63] and even in high-risk individuals who subsequently develop affective psychosis rather than schizophrenia.[64] Direct comparisons of patients with schizophrenia and bipolar disorder confirm the presence of more distributed gray matter deficits in schizophrenia, especially in the posterior cingulate cortex[65] and inferior, middle, and superior frontal regions.[66] Our observations suggest that, at least in part, these gray matter deficits may be driven by the presence of hypogyria in nonaffective psychoses.

Although the exact mechanisms behind formation of cortical folds remain unclear, the adult pattern of gyrification seems tightly linked to the integrity of corticocortical and corticosubcortical connectivity in the developing brain.[18] In this context, it is likely that a higher loading of neurodevelopmental aberrations is present in the pathophysiology of psychosis

in subjects who do not respond to treatment. Relevant to this notion is the observation that neurological soft signs, often considered to be an index of neurodevelopmental disturbances in schizophrenia,[67] are related to both reduced gyrification[68] and poor response to antipsychotics in psychosis.[69] Moreover, unlike responders, the nonresponders showed no diagnostic differences in gyrification. The presence of marked hypogyria, alongside the lack of diagnosis-related differences in gyrification in the nonresponders, suggests that as a group, nonresponders are likely to have a more homogeneous pathophysiological process underlying psychosis than the responders. Consistent with this finding, Penttilä et al[70] observed an association between reduced cortical folding and treatment resistance in bipolar disorder and concluded that in affective disorders, poor treatment response may be driven by neurodevelopmental anomalies. Reduced gyrification may also result from an atrophic process affecting the gray matter, at least in certain frontal clusters in the nonaffective group, in which progressive gray matter reduction has been shown to be maximal in schizophrenia.[71] This issue warrants further investigation of longitudinal changes in gyrification in psychosis.

Several mechanisms may underlie our observation of extensive gyrification defects in nonresponders. On one hand, nonresponders may represent a distinct group of patients in whom a specific pathophysiological substrate underlies the development of psychosis. Cortical folding shows the highest activity during intrauterine growth and early infancy.[18] Nonresponders may have experienced a pathophysiological insult at an earlier phase of the neurodevelopmental trajectory than the responders, leading to extensive hypogyria in adult life. Psychosis in nonresponders may be associated with an aberration in the molecular and genetic factors that determine axonal integrity, which in turn influences cortical gyrification.[72] It is also possible that nonresponders represent a subset of patients with a more severe form of the same underlying disease process. Nevertheless, the brain regions showing gyrification defects in patients with FEP as a whole (when compared with healthy controls) were distinct from the regions showing gyrification abnormalities in nonresponders (when compared with responders). This suggests the presence of a distinct set of cortical neurodevelopmental abnormalities that contribute to poor prognosis in FEP.

Our study has a number of strengths. Unlike the curvature-based methods used in some studies,[73,74] the method by Schaer and colleagues that we used provides a composite index that captures both the curvature or depth and the spatial frequency or density of sulcogyral patterns on the cortical surface. Hence, the hypogyric regions we observed could reflect either a reduced number of sulcal formations or an increased width and reduced depth of the sulci themselves. Future investigations focusing on sulcal frequency as well as the LGI can clarify the exact nature of the gyrification defects in the nonresponders. A number of previous studies seeking to identify structural predictors of treatment response included extensively medicated subjects,[5,9,52] while our sample consisted of patients who were either unmedicated or minimally medicated before scanning. Further, the results of our post hoc analysis comparing medication-naive subjects with a subset of medication-exposed subjects (eAppendix and eTable in Supplement) suggest that the changes we observed are unlikely to be explained by the use of antipsychotics.

In terms of limitations, the surface-based morphometric approach that we used is limited to the cortical mantle and does not provide information on deep gray matter structures such as the striatum, which have been previously associated with treatment response in psychosis.[9] Also, the cross-sectional nature of our study precludes firm conclusions as to the timing of the gyrification defects, and the assumption regarding their neurodevelopmental origin must be considered with caution. The use of a dichotomous treatment response variable can also be seen as a limitation, but this allows our results to be considered in line with antipsychotic clinical trials and neuroimaging studies investigating treatment response. By investigating the relationship between vertexwise gyrification and treatment response for the first time, we have established that the hypothesized relationship is indeed present in several brain regions in FEP. In the future, the application of statistical discriminant approaches such as support vector machine[75] could confirm whether an optimal combination of these distributed surface anatomical changes could satisfactorily classify the prospective responders from the nonresponders using an independent set of test data.

Our study provides crucial evidence of neuroimaging markers that can be used early in psychosis to predict prognosis in clinical settings. Identifying putative poor responders at the outset could assist in stratified treatment plans at an individual level and with appropriate resource allocation at the service level. Furthermore, the identification of cortical surface morphology and connectivity markers that characterize poor response opens the question as to whether risk factors that affect cortical surface morphology and integrity could be used to improve the proportion of patients responding to antipsychotic treatment at the first episode.

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