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Contrasting Case-Control and Normative Reference Approaches to Capture Clinically Relevant Structural Brain Abnormalities in Patients With First-Episode Psychosis Who Are Antipsychotic Naive

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IMPORTANCE To make progress toward precision psychiatry, it is crucial to move beyond case-control studies and instead capture individual variations and interpret them in the context of a normal range of biological systems.

OBJECTIVE To evaluate whether baseline deviations from a normative reference range in subcortical volumes are better predictors of antipsychotic treatment response than raw volumes in patients with first-episode psychosis (FEP) who were naive to antipsychotic medication.

DESIGN, SETTING, AND PARTICIPANTS In this prospective longitudinal study, patients with first-episode psychosis who were referred from different clinical settings (emergency department, inpatient units, and outpatient clinics) at the University of Alabama at Birmingham were included. A total of 286 patients were screened, 114 consented, 104 enrolled in the treatment trial, and 85 completed the trial. Patients were observed for 16 weeks. Controls were matched by age and sex. Data were collected between June 2016 and July 2021, and data were analyzed from August 2021 to June 2022.

INTERVENTIONS Risperidone on a flexible dosing scheme for 16 weeks. There was an option to switch to aripiprazole for excessive adverse effects.

MAIN OUTCOMES AND MEASURES The main outcome of this study was to evaluate, in patients with FEP who were naive to antipsychotic medication, the association of baseline raw volumes and volume deviations in subcortical brain regions with response to antipsychotic medication. Raw brain volumes or volume deviation changes after treatment were not examined.

RESULTS Of 190 included participants, 111 (58.4%) were male, and the mean (SD) age was 23.7 (5.5) years. Volumes and deviations were quantified in 98 patients with FEP, and data from 92 controls were used as comparison for case-control contrasts and reference curve calibration. In case-control contrasts, patients with FEP had lower raw thalamus ($P = .002$; $F = 9.63$; $df = 1$), hippocampus ($P = .009$; $F = 17.23$; $df = 1$), amygdala ($P = .01$; $F = 6.55$; $df = 1$), ventral diencephalon ($P = .03$; $F = 4.84$; $df = 1$), and brainstem volumes ($P = .004$; $F = 8.39$; $df = 1$). Of 98 patients, 36 patients with FEP (36%) displayed extreme deviations. Associations with treatment response significantly differed between raw volume and deviation measures in the caudate ($z = -2.17$; $P = .03$) and putamen ($z = -2.15$; $P = .03$).

CONCLUSIONS AND RELEVANCE These data suggest that normative modeling allows capture of interindividual heterogeneity of regional brain volumes in patients with FEP and characterize structural pathology in a clinically relevant fashion. This holds promise for progress in precision medicine in psychiatry, where group-level studies have failed to derive reliable maps of structural pathology.

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Supplemental content

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The premise of precision medicine is that an individual's unique physiologic characteristics, environment, and lifestyle play a significant role in disease vulnerability and response to specific therapies.[1] To make progress toward this goal, it is imperative to move beyond group-based studies that disregard individual variations as noise[2] and instead interpret them in the context of the normal range of biological systems.

Several neuroimaging methods have been developed to assess pathology in psychiatric disorders in contrast to a normal range, most commonly in the context of brain aging.[3,4] Here, we use normative modeling (brain growth charting) to characterize disease signatures at the individual level,[5] where positive (higher volumes compared with the normative range) and negative (lower volumes compared with the normative range) deviations can be calculated for each individual. Recent applications have shown substantial heterogeneity in structural brain abnormalities and that group averages do not accurately reflect patterns of atypicality at the individual level.[6-8] However, it is unclear if these structural deviations map onto clinical outcomes.

We enrolled antipsychotic medication–naive patients with first-episode psychosis (FEP) in a 16-week trial with risperidone and quantified raw subcortical and ventricle volumes as well as deviations from a normative reference model at baseline. We chose subcortical regions because they include principal sites of dopaminergic drug action and ventricles because these are a hallmark structural feature in schizophrenia. We hypothesized that volume deviations would be heterogeneous and that deviations in subcortical regions would be superior to raw volumes in predicting treatment response.

Key Points

Question Can normative modeling be used to quantify structural brain pathology in a way that is better suited than raw volume measures in predicting antipsychotic treatment response in patients with first-episode psychosis who were naive to antipsychotic medication?

Findings In this study including 98 patients, negative brain volume deviations were associated with better antipsychotic treatment response compared with raw subcortical volumes. The caudate, putamen, and ventral diencephalon, 3 key dopaminergic regions, were the most relevant associated factors.

Meaning These data suggest that normative modeling allows capture of interindividual heterogeneity of regional brain volumes in patients with first-episode psychosis and characterize structural pathology in a clinically relevant fashion.

Methods

This University of Alabama at Birmingham Institutional Review Board–approved study design was previously described,[9] and written informed consent was obtained from all participants (eFigure 1 in the Supplement). We recruited patients with FEP from clinical sites at the University of Alabama at Birmingham and controls via advertisements (**Table**). Data on race and ethnicity were self-reported. Participants were excluded if they had significant medical conditions, substance use disorders (except nicotine or cannabis use), or magnetic resonance imaging contraindications. Patients were naive to antipsychotic medications or had no more than 5 days of lifetime antipsychotic exposure. Controls with a personal history of a mental illness or family history of psychosis in a first-degree relative were excluded. Consensus diagnoses were established by 2 psychiatrists (A.C.L. and N.V.K.). Patients with FEP entered into a 16-week trial of risperidone using a flexible dose regimen, with an option to switch to aripiprazole if indicated. Symptom severity was assessed using the Brief Psychiatric Rating Scale; treatment response was calculated as percentage improvement of positive symptoms from baseline to end point.

Imaging was performed on a 3-T Siemens Magnetom Prisma equipped with a 20-channel head coil. Structural images were acquired using a magnetization-prepared rapid gradient echo sequence (repetition time, 2400 milliseconds; time to echo, 2.22 milliseconds; inversion time, 1000 milliseconds; 0.8 mm^3 voxels), and sampling perfection with application-optimized contrasts using different flip angle evolution sequence (repetition time, 3200 milliseconds; time to echo, 56 milliseconds; 0.8 mm^3 voxels). Data were processed in FreeSurfer version 7.1.1.[10] We quantified subcortical and ventricle volumes, adding left and right volumes for bilateral regions. We quantified individual deviations for each region (and averaged those for bilateral regions) based on a normative reference model (n = 58 836) using the Predictive Clinical Neuroscience and brain charts toolkits (**Figure 1**).[11] We used control data to calibrate normative curves.[12] We also computed extreme deviations (2 or more SDs).

To examine demographic differences we used 2-tailed *t* tests continuous variables and χ^2 analyses for categorical variables. We used a multivariate general linear model with raw volumes as dependent variables, group as fixed factor, and age and sex as covariates, followed by post hoc analyses to determine which regions differed between groups. We used Bonferroni corrections to account for multiple comparisons in post hoc analyses. We considered a *P* value of <.05 to be significant. We performed partial correlations between raw volumes and treatment response (age and sex as covariates), and Pearson correlations between deviations and treatment response.

Results

Of 190 included participants, 111 (58.4%) were male, and the mean (SD) age was 23.7 (5.5) years. Phenotypic characteristics are detailed in the Table.

Raw volume measures significantly differed between groups when variables were considered jointly on all measures (Pillai trace = 0.18; $F = 3.23$; $P < .001$). Post hoc analyses demonstrated that FEP had lower thalamus ($F = 9.63$; $P < .01$), hippocampus ($F = 17.23$; $P < .01$), amygdala ($F = 6.55$; $P = .01$), ventral diencephalon ($F = 4.84$; $P = .03$), and brainstem volumes ($F = 8.39$; $P < .01$). Ventricle volumes did not differ between groups (eFigure 2 in the Supplement).

Table. Demographic and Clinical Measures

Measure	No. (%) Patients with FEP (n = 98)	No. (%) HCs (n = 92)	Test	*P* value
Demographic variables				
Sex				
Male	60 (61.2)	51 (55.4)	χ^2 = 0.66	.42
Female	38 (38.8)	41 (44.6)		
Age, mean (SD), y	23.42 (5.67)	23.90 (5.44)	*t* = 0.79	.55
Parental occupation, mean (SD)[a]	5.45 (4.77)	4.13 (3.74)	χ^2 = 11.68	.04
Race and ethnicity[b]				
African American	56 (57.1)	21 (22.8)	NA	NA
American Indian	<5	0		
Asian	<5	14 (15.2)		
Hispanic	<5	3 (2)		
Multiracial	<5	0		
Pacific Islander	0	<5		
White	37 (37.8)	53 (57.8)		
Other	0	<5		
Clinical variables				
Diagnosis				
Schizophrenia	48 (49)	NA	NA	NA
Schizoaffective disorder	17 (17.3)	NA	NA	NA
Schizophreniform disorder	6 (6.1)	NA	NA	NA
Brief psychotic disorder	4 (4.1)	NA	NA	NA
Bipolar disorder with psychosis	4 (4.1)	NA	NA	NA
Major depression with psychosis	3 (3.1)	NA	NA	NA
Unspecified psychosis	16 (16.3)	NA	NA	NA
DUP, mean (SD), mo	23.60 (40.15)	NA	NA	NA
UDS positive for cannabis	33 (33.7)	NA	NA	NA
Prior antipsychotic exposure	20 (20.4)	NA	NA	NA
Risperidone dose at week 16, mean (SD), mg[c]	4.39 (2.52)	NA	NA	NA
BPRS[d]				
Baseline				
Total	48.26 (11.41)	NA	NA	NA
Positive	15.15 (3.97)	NA	NA	NA
Negative	5.48 (3.02)	NA	NA	NA
Week 16				
Total	29.54 (6.17)	NA	NA	NA
Positive	6.39 (2.95)	NA	NA	NA
Negative	5.33 (2.70)	NA	NA	NA

Abbreviations: BPRS, Brief Psychiatric Rating Scale; DUP, duration of untreated psychosis; FEP, first-episode psychosis; HC, healthy control; NA, not applicable; UDS, urine drug screen.

[a] Ranks determined from *Diagnostic Interview for Genetic Studies* (scale ranges from 1 to 18); higher rank (lower numerical value) corresponds to higher socioeconomic status.

[b] Race and ethnicity were based on participant self-report.

[c] Four patients were switched to aripiprazole prior to week 16 and were not included in the average antipsychotic medication dose at week 16, and 2 patients opted not to be treated with antipsychotic medication.

[d] BPRS ranged from 1 to 7; positive (conceptual disorganization, hallucinatory behavior, suspiciousness and unusual thought content); negative (emotional withdrawal, motor retardation, and blunted affect). Higher scores indicate greater symptom severity.

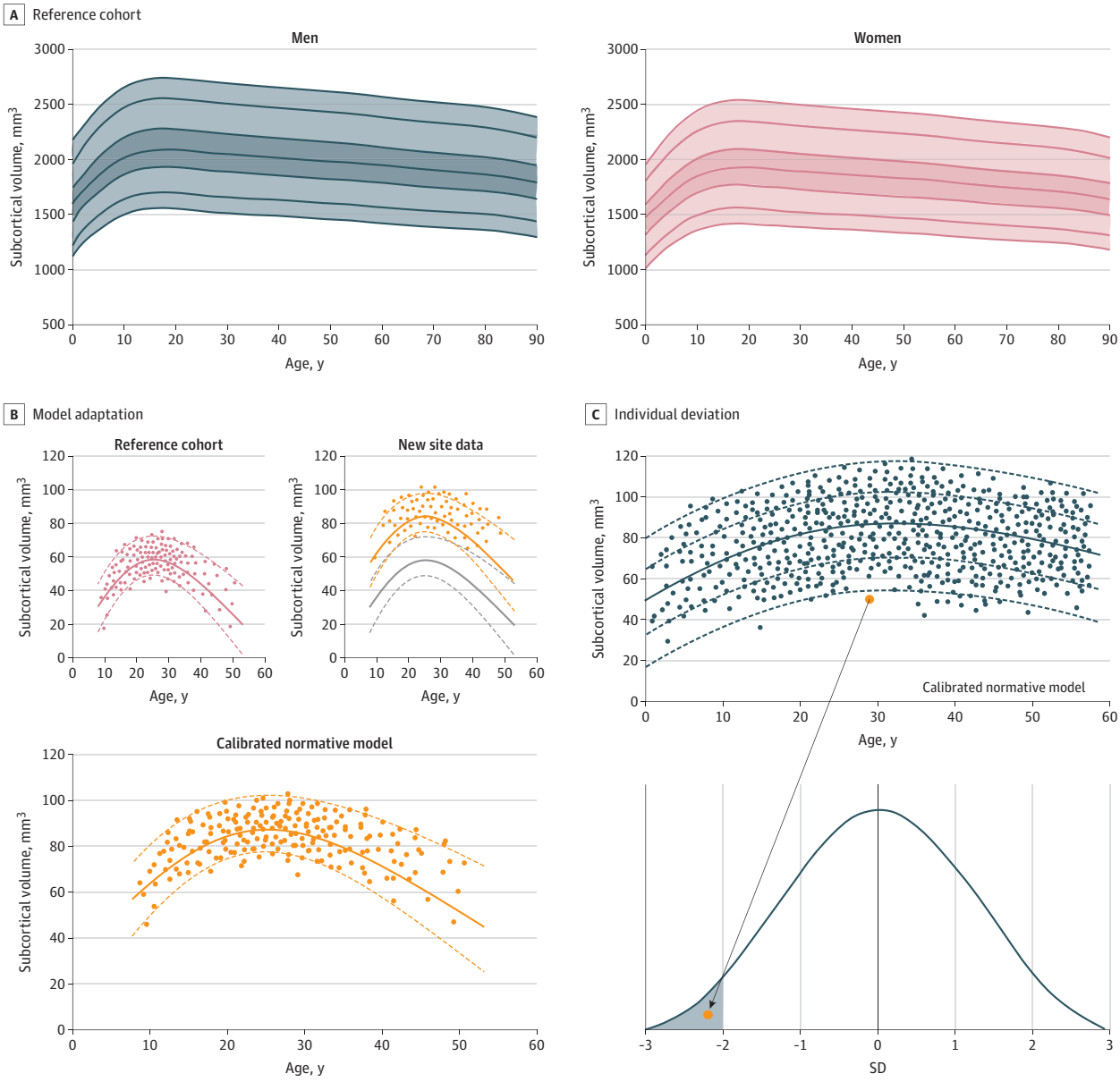
Across regions, 36 of 98 patients with FEP (36%) displayed extreme deviations; 21 (22%) had extreme deviations in ventricles and 21 (22%) had extreme deviations in subcortical regions. Extreme deviations were shared among patients more commonly in ventricle regions (6% to 9% of patients with FEP) compared with subcortical regions (0% to 5% of patients with FEP). Extreme deviations were twice as likely to be in the negative than positive direction in subcortical regions, whereas 13 of 21 individuals with extreme ventricle deviations (62%) had deviations in the positive direction (**Figure 2**A-C). The number of deviations did not differ between patients who did or did not use cannabis.

While subcortical raw volumes at baseline were not associated with response, deviations in the caudate, putamen, and ventral diencephalon were (Figure 2D-E). For these regions, correlations significantly differed between raw volume and deviation measures in the caudate (z = −2.17; P = .03) and putamen (z = −2.15; P = .03). Ventricle raw volumes or deviations were not associated with response.

Discussion

In this study, we report that structural deviations from a normative model in subcortical and ventricle regions are heterogeneous in antipsychotic-naive patients with FEP. We extend the literature by providing empirical evidence that negative deviations in key dopaminergic brain regions are more likely

Figure 1. Study Overview

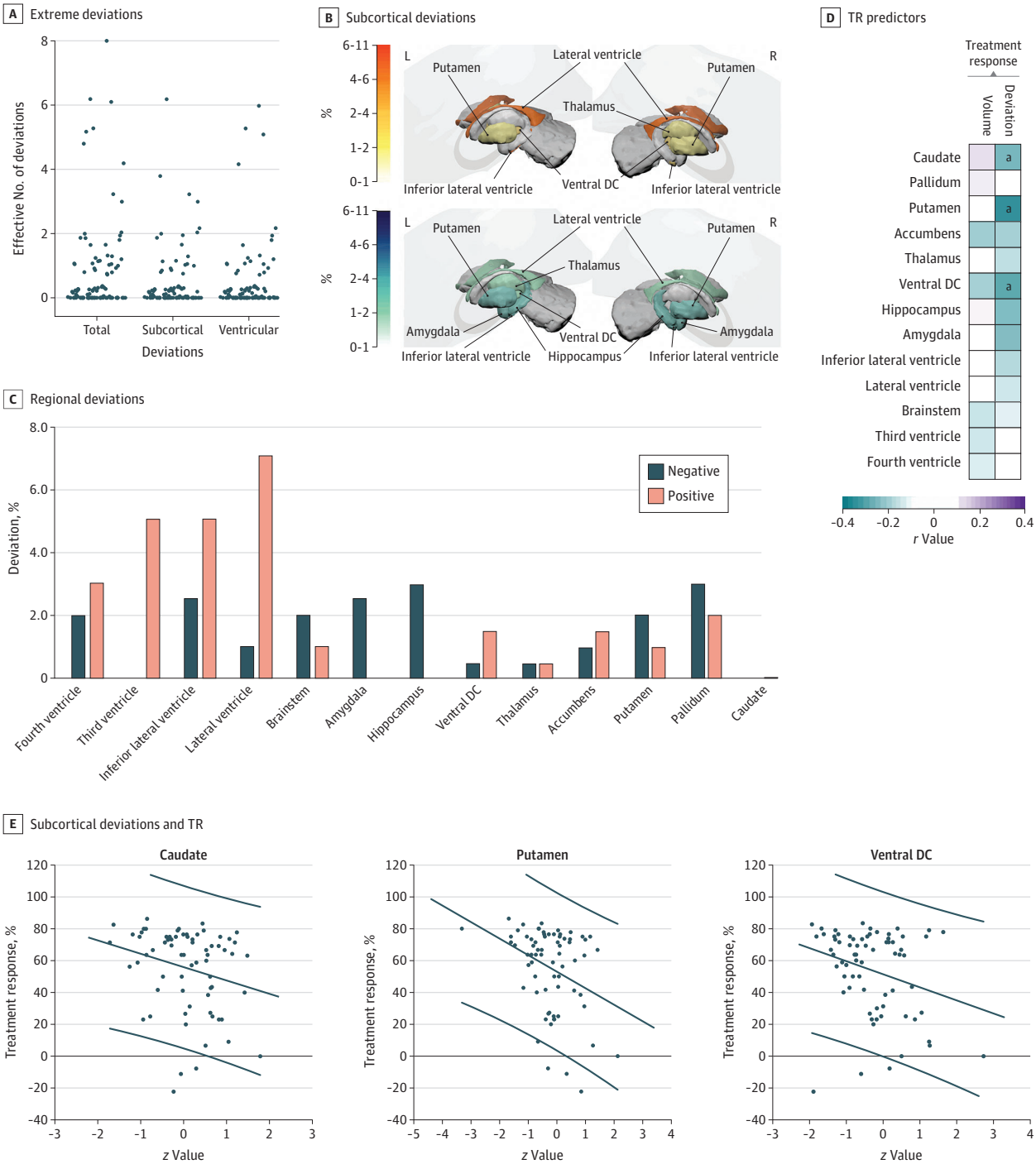


A, Normative modeling is a framework where individual-level statistical inferences are made with respect to the normative reference. The normative reference is based on a large cohort of individuals across the life span. B, Normative models can be applied to new data sets. To transfer the normative models to new sites, healthy controls from the new data set are used to learn site effects. During calibration, the shape of the curve remains unchanged (because the life span trajectories of region-level brain volumes are the same, regardless of which scanner is used), but the scale and the intercept are adjusted to fit the new data set. C, Plotting individuals on a calibrated normative model allows for calculation of a z-value which shows how many standard deviations the individual is away from the mean.

associated with treatment response in patients with FEP than raw volumes, suggesting that structural deviations may be more reflective of clinically relevant pathology. Our data suggest that normative modeling allows us to capture interindividual heterogeneity and characterize structural pathology in a clinically relevant fashion in patients with FEP.

Consistent with recent reports, we found that anatomical loci differ across patients to the extent that group average disguises interindividual differences.[7] Most prominently, ventricle volumes were not abnormal in case-control analyses, but extreme ventricle deviations were noted in 22% of patients with FEP. While extreme positive deviations in ventricles were most common, surprisingly, 9% of patients had extreme negative deviations, which, to our knowledge, has not been reported to date. This as yet poorly understood heterogeneity may relate to both the etiology and prognosis in this complex neuropsychiatric syndrome.

Figure 2. Structural Abnormalities in Subcortical and Ventricle Regions in Antipsychotic Medication–Naive Patients With First-Episode Psychosis



A, Effective number of extreme deviations (2 SDs or more) in subcortical and ventricle volumes in patients with first-episode psychosis in relation to a normative reference cohort. B, Percentage of patients with first-episode psychosis who show extreme deviations in volumes from the reference cohort for individual brain regions. Deviations were categorized as positive when the volume was greater than that of the reference cohort (upper image); deviations were categorized as negative when the volume was smaller than that of the reference range (lower image). C, Graphic representation of extreme positive and negative deviations. D, Correlation matrix. The left column shows the association between subcortical/ventricle volumes and treatment response (TR); the right column shows the association between subcortical/ventricle deviations (SD) and TR. E, Scatterplots depicting correlations between caudate deviations and TR as well as putamen deviations and TR and ventral diencephalon deviations and TR. Diagonal lines indicate best fit line (center line) and 95% CI (upper and lower lines). DC indicates diencephalon.

[a] Significant values.

We also found that negative deviations in key dopaminergic brain regions are more likely associated with subsequent treatment response in patients with FEP compared with raw volumes. Greater negative deviations of the ventral diencephalon (which contains the substantia nigra), caudate, and putamen were most predictive of favorable treatment response in our cohort. This is perhaps not surprising, given recent advances suggesting that dopaminergic dysregulation in schizophrenia is greatest in the nigrostriatal as opposed to the mesolimbic pathway.[13] Positron emission tomography imaging has found that persons with less endogenous dopamine have larger striatal volumes,[14] and antipsychotic medication treatment in patients with FEP has shown to increase striatal volumes (which was correlated with a reduction in positive symptom severity).[15] Taken together, it is tempting to speculate that negative deviations from the reference range in these regions reflect dopamine dysfunction, which is reversible with antipsychotic treatment.

Strengths and Limitations

One of the strengths is the enrollment of patients with FEP who were naive to antipsychotic medication, which mitigates confounds of illness chronicity and prior medication exposure. Our retention rates were excellent, with only approximately 18% attrition in those who entered the medication trial. Another strength is that more than 60% of patients identified as racial and ethnic minorities, groups that have historically lacked equitable inclusion in medical research.

This study has limitations. We did not exclude patients who used cannabis, a major risk factor for developing psychosis, as this would have limited the generalizability of our data. We included age and sex, the same variables relevant in normative modeling, rather than total intracranial volumes as covariates when computing correlations between raw volumes and treatment response. We did this to be consistent in variables considered for both models. Using total intracranial volume for raw data did not change these results (data not shown).

Conclusions

Taken together, the normative modeling approach holds promise for progress in precision medicine in psychiatry where group-level studies have failed to provide reliable maps of structural pathology.

ARTICLE INFORMATION

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Correction: This article was corrected on December 7, 2022, to change the article to open access status under the CC-BY License.

Author Contributions: Dr Kraguljac had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Ms Remiszewski and Dr Bryant contributed equally to this work
Study concept and design: Marquand, Kraguljac.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Remiszewski.
Critical revision of the manuscript for important intellectual content: Bryant, Rutherford, Marquand, Nelson, Askar, Lahti, Kraguljac.
Statistical analysis: Remiszewski, Bryant, Rutherford, Marquand, Nelson.
Obtained funding: Lahti.
Study supervision: Kraguljac.

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REFERENCES

1. Ozomaro U, Wahlestedt C, Nemeroff CB. Personalized medicine in psychiatry: problems and promises. *BMC Med*. 2013;11:132. doi:10.1186/1741-7015-11-132

2. Kapur S, Phillips AG, Insel TR. Why has it taken so long for biological psychiatry to develop clinical tests and what to do about it? *Mol Psychiatry*. 2012;17(12):1174-1179. doi:10.1038/mp.2012.105

3. Ryan MC, Hong LE, Hatch KS, et al. The additive impact of cardio-metabolic disorders and psychiatric illnesses on accelerated brain aging. *Hum Brain Mapp*. 2022;43(6):1997-2010. doi:10.1002/hbm.25769

4. Chen CL, Hwang TJ, Tung YH, et al. Detection of advanced brain aging in schizophrenia and its structural underpinning by using normative brain age metrics. *Neuroimage Clin*. 2022;34:103003. doi:10.1016/j.nicl.2022.103003

5. Marquand AF, Kia SM, Zabihi M, Wolfers T, Buitelaar JK, Beckmann CF. Conceptualizing mental disorders as deviations from normative functioning. *Mol Psychiatry*. 2019;24(10):1415-1424. doi:10.1038/s41380-019-0441-1

6. Wolfers T, Beckmann CF, Hoogman M, Buitelaar JK, Franke B, Marquand AF. Individual differences *v.* the average patient: mapping the heterogeneity in ADHD using normative models. *Psychol Med*. 2020;50(2):314-323. doi:10.1017/S0033291719000084

7. Wolfers T, Doan NT, Kaufmann T, et al. Mapping the heterogeneous phenotype of schizophrenia and bipolar disorder using normative models. *JAMA Psychiatry*. 2018;75(11):1146-1155. doi:10.1001/jamapsychiatry.2018.2467

8. Zabihi M, Oldehinkel M, Wolfers T, et al. Dissecting the heterogeneous cortical anatomy of autism spectrum disorder using normative models. *Biol Psychiatry Cogn Neurosci Neuroimaging*. 2019;4(6):567-578. doi:10.1016/j.bpsc.2018.11.013

9. Kraguljac NV, Anthony T, Morgan CJ, Jindal RD, Burger MS, Lahti AC. White matter integrity, duration of untreated psychosis, and antipsychotic treatment response in medication-naïve first-episode psychosis patients. *Mol Psychiatry*. 2021;26(9):5347-5356. doi:10.1038/s41380-020-0765-x

10. Fischl B. FreeSurfer. *Neuroimage*. 2012;62(2):774-781. doi:10.1016/j.neuroimage.2012.01.021

11. Rutherford S, Fraza C, Dinga R, et al. Charting brain growth and aging at high spatial precision. *Elife*. 2022;11:e72904. doi:10.7554/eLife.72904

12. Dinga R, Fraza CJ, Bayer JMM, Kia SM, Beckmann CF, Marquand AF. Normative modeling of neuroimaging data using generalized additive models of location and shape. *bioRxiv*. Preprint posted online June 14, 2021. doi:10.1101/2021.06.14.448106

13. McCutcheon RA, Abi-Dargham A, Howes OD. Schizophrenia, dopamine and the striatum: from biology to symptoms. *Trends Neurosci*. 2019;42(3):205-220. doi:10.1016/j.tins.2018.12.004

14. Caravaggio F, Ku Chung J, Plitman E, et al. The relationship between subcortical brain volume and striatal dopamine $D_{2/3}$ receptor availability in healthy humans assessed with [^{11}C]-raclopride and [^{11}C]-(+)-PHNO PET. *Hum Brain Mapp*. 2017;38(11):5519-5534. doi:10.1002/hbm.23744

15. Andersen HG, Raghava JM, Svarer C, et al. Striatal volume increase after six weeks of selective dopamine $D_{2/3}$ receptor blockade in first-episode, antipsychotic-naïve schizophrenia patients. *Front Neurosci*. 2020;14:484. doi:10.3389/fnins.2020.00484