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Cortical and Subcortical Structural Morphometric Profiles in Individuals with Nonaffective and Affective Early Illness Psychosis

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Research has found strong evidence for common and distinct morphometric brain abnormality profiles in nonaffective psychosis (NAff-P) and affective psychosis (Aff-P). Due to chronicity and prolonged medication exposure confounds, it is crucial to examine structural morphometry early in the course of psychosis. Using Human Connectome Project-Early Psychosis data, multivariate profile analyses were implemented to examine regional profiles for cortical thickness, cortical surface area, subcortical volume, and ventricular volume in healthy control (HC; $n = 56$), early illness NAff-P ($n = 83$), and Aff-P ($n = 30$) groups after accounting for normal aging. Associations with symptom severity, functioning, and cognition were also examined. Group regional profiles were significantly nonparallel and differed in level for cortical thickness ($P < .001$), with NAff-P having widespread cortical thinning relative to HC and Aff-P and some regions showing greater deficits than others. Significant nonparallelism of group regional profiles was also evident for cortical surface area ($P < .006$), with Aff-P and N-Aff-P differing from HC and from each other ($P < .001$). For subcortical volume, there was significant profile nonparallelism with NAff-P having an enlarged left pallidum and smaller accumbens and hippocampus ($P < .028$), and Aff-P having a smaller accumbens and amygdala ($P < .006$), relative to HC. NAff-P also had larger basal ganglia compared to Aff-P. Furthermore, NAff-P had enlarged ventricles ($P < .055$) compared to HC and Aff-P. Additionally, greater ventricular volume was associated with increased manic symptoms in NAff-P and Aff-P. Overall, this study found common and distinct regional morphometric profile abnormalities in early illness NAff-P and Aff-P, providing evidence for both shared and disease-specific pathophysiological processes.

Key words: MRI/structural morphometry/early illness psychosis/profile analysis

Introduction

Morphometric brain abnormalities have been consistently reported in nonaffective psychosis (NAff-P)[1–8] and affective psychosis (Aff-P) across the illness course[5–7,9–14], with strong evidence for common and distinct profiles of abnormalities[10,14–17]. Knowledge of commonalities and differences could elucidate pathophysiological changes underlying psychosis in general, as well as the unique pathophysiological changes underlying NAff-P and Aff-P. However, illness chronicity and prolonged medication exposure can confound this relationship.[5,6,13] Given these confounds, and the importance of early intervention, the current study analyzed Human Connectome Project-Early Psychosis (HCP-EP) morphometric brain profile data from NAff-P and Aff-P patients within 5 years of psychosis onset, as well as healthy controls (HC). In particular, we examined cortical thickness, cortical surface area, subcortical volume, and ventricular volume profiles.

The relatively few studies examining these brain morphometry measures in early illness NAff-P and Aff-P individuals have identified both common abnormalities and important morphometric distinctions.[18] Compared to HC, NAff-P and Aff-P individuals have consistently shown cortical thinning,[19–25] with widespread changes in frontotemporal regions for NAff-P.[24,26,27] In contrast, few studies have examined cortical surface area. For NAff-P, relative to HC, one study found no group differences.[21] For Aff-P, one study examined gray matter boundary complexity (i.e., proxy surface area measure) and found no difference relative to HC.[28] Thus, while both early psychosis groups show cortical thinning, the groups differ somewhat in regional patterns of thinning, and it remains unclear whether groups differ from HC or each other in regional surface area profiles.

Arguably, the most distinct structural differences between early psychosis groups are in subcortical and ventricular regions of interest (ROI). NAff-P, but not Aff-P, is characterized by reduced hippocampal[7,27,29–31] enlarged caudate,[32] and enlarged ventricular volumes.[21,33,34] In contrast, Aff-P has been characterized by amygdala volume abnormalities.[7,31,35–38] Although directionality of amygdala findings have been mixed,[36] it has been posited that discrepancies could be attributed to medication, particularly lithium.[7,35–37] Studies with Aff-P lithium-naïve/unmedicated individuals have found reduced amygdala volumes compared to HC[37,39] and Aff-P individuals taking lithium.[39,40]

We also examined associations between structural morphometry and clinical symptom severity, functioning, and cognition. Previous early psychosis studies have reported functioning[41–43] and cognitive deficits[41,42,44]; however, it is unclear how these measures are associated with structural morphometry. Symptom severity has not been consistently associated with structural morphometry,[19,45] whereas better cognition has been associated with increased cortical thickness and surface area, with stronger support for increased prefrontal and temporal regions[45–50] (note Hartberg et al[49] found working memory to be inversely associated with cortical thickness) and smaller ventricular volumes.[51,52]

The current study aim was to examine commonalities and differences in morphometric profiles in the early stages of NAff-P and Aff-P. Using multivariate profile analyses,[53] we examined whether ROI profiles differed in overall "level" or showed significant "nonparallelism" (i.e., pattern differences) for cortical thickness, cortical surface area, subcortical volume, and ventricular volume in HC, NAff-P, and Aff-P groups. We also examined whether clinical symptom severity, functioning, and cognitive measures were differentially or similarly related to overall levels and regional patterns of morphometric profiles. Previous studies with multiple clinical groups have used this multivariate profile analysis approach.[54–57] However, while nonparallel profiles have been reported when comparing individuals with schizophrenia to neurotypical individuals[57] or individuals with alcoholism (Mathalon et al, 2003), no previous study has compared morphometric profiles of early psychosis groups. In the current study, we hypothesized:

1. Early psychosis would show level and parallelism differences relative to HC, with more pronounced differences for NAff-P than Aff-P.
2. Early psychosis groups would show differences in level and parallelism relative to each other. NAff-P would show greater deficit (or excess in the case of ventricular ROIs) in the level of their ROI profiles relative to Aff-P. Additionally, we predicted that the NAff-P ROI profile would have relatively increased basal ganglia volume and decreased hippocampal volume, and that the Aff-P profile would have relatively reduced amygdala volume.
3. Higher cognitive scores would be associated with greater cortical thickness and surface area of frontotemporal regions and decreased ventricular volume within early psychosis. Symptom severity and global functioning would not be associated with morphometric measures.

Methods

Participants

HC ($n = 56$), NAff-P ($n = 83$), and Aff-P ($n = 30$) participants were scanned at one of three sites (Indiana University [$n = 80$], Brigham and Women's Hospital [$n = 46$], and McLean Hospital [$n = 43$]) as part of the Human Connectome Project-Early Psychosis (HCP-EP; doi:10.15154/1524263). NAff-P participants met DSM-5[58] criteria for schizophrenia ($n = 58$), schizophreniform ($n = 9$), schizoaffective ($n = 11$), psychosis not otherwise specified ($n = 3$), delusional disorder ($n = 1$), or brief psychotic disorder ($n = 1$), with onset within five years prior to study entry. Aff-P participants met DSM-5 criteria for major depression with psychosis (single and recurrent episodes; $n = 6$) or bipolar disorder with psychosis (including most recent episode depressed and manic types; $n = 24$) with onset within five years prior to study entry. In early psychosis groups, illness duration, medication information, and comorbid substance use disorders were assessed based on clinical interview. See supplemental methods for additional inclusion/exclusion criteria.

Clinical Measures

In early psychosis groups, general psychopathology and positive symptoms were assessed using the Positive and Negative Syndrome Scale[59] (PANSS). PANSS Marder[60] symptom factors (Positive, Negative, Cognitive) were calculated. Negative symptoms were further assessed using the Clinical Assessment Interview for Negative Symptoms[61–63] (CAINS) subscales of Motivation and Expression. Mania and depression severity were assessed using the Young Mania Rating Scale[64] (YMRS) and the Montgomery-Asberg Depression Rating Scale[65] (MADRS), respectively. Global symptoms, role, and social functioning were assessed with the Global Assessment of Functioning[66] (GAF) scale. Vocabulary and matrix reasoning were assessed using the WASI-II.[67]

Procedure

Procedures were approved by the Partners Healthcare Human Research Committee/IRB and complied with the Declaration of Helsinki. Participants provided written informed consent, or in the case of minors, parental written consent and participant assent.

Structural MRI Acquisition and Processing

To achieve harmonization of brain scan data across sites, all sites used a Siemens Prisma 3T MRI scanner, implemented identical scan sequences and protocols, and did not upgrade scanner software or hardware during the study period. Furthermore, MRI phantoms were scanned repeatedly at each site, including at the beginning and the end of the study, to monitor MRI sequence stability over the study period. Sites were trained by four study staff who traveled to two or three of the sites and underwent the scan protocol. Scan data were inspected to ensure that scans from the same individual looked similar between sites. However, these travelling scans were not used to derive quantitative correction factors to harmonize data. To account for possible site variation, our statistical model for generating z-scores adjusted for scan site, as well as age, gender, and intracranial volume (ICV), as described below. High-resolution structural T1-weighted images were acquired based on: repetition time (TR) = 2,400 ms, echo time (TE) = 2.22 ms, field of view (FOV) = 256 mm, and slice thickness = 0.80 mm.

Structural MRI images were processed using HCP's minimal preprocessing pipeline (full details in Glasser et al[68]). In brief, this pipeline used FreeSurfer (version 6.0) to segment the brain into cortical ROIs using the Desikan–Killiany Atlas[69] and subcortical and ventricular ROIs using FreeSurfer's atlas.[70] Consistent with multi-site ENIGMA studies that argued for analytic standardization,[5,6] the same FreeSurfer-provided ROI parcellations were used. Thickness and surface area of cortical regions (68 unilateral ROIs–34 in each hemisphere), and volumes of subcortical (14 unilateral ROIs–7 in each hemisphere) and ventricular (5 unilateral ROIs–2 in each hemisphere, plus third ventricle) regions were calculated.

Analyses

Z-scoring Adjustment Procedure

Effects of normal brain maturation[71] (i.e., age), sex,[72–75] scanning site (three sites), and ICV[72,76,77] were statistically removed using a regression model, similar to our prior studies (see supplemental methods for details).[78,79] ICV was not removed for cortical thickness ROIs since ICV is not as strongly correlated with cortical thickness[72] (FreeSurfer guidelines, https://surfer.nmr.mgh.harvard.edu/fswiki/eTIV). Interpretation of adjusted z-scores is straightforward: each morphometric measure's adjusted z-score represents the participant's deviation, in standard units, from the expected value for a HC of the same age, sex, scanning site, and in the case of area and volume measures, ICV. Adjusted z-scores were used in all analyses.

Structural Morphometric Profile Analyses

Using repeated measures multivariate analyses of variance (rmMANOVAs),[53] group profile differences were

assessed within each morphometric measure: (1) cortical thickness, (2) cortical surface area, (3) basal ganglia volume (caudate, putamen, pallidum), (4) subcortical volume (accumbens, hippocampus, amygdala, thalamus), and (5) ventricular volume. Because prior studies have shown basal ganglia enlargement in schizophrenia,[2,6] an effect attributed to antipsychotic medication,[80–82] basal ganglia profiles were analyzed separately from other subcortical ROIs typically showing reductions in schizophrenia. Groups were compared on two profile aspects: (1) parallelism (i.e., multivariate Group × Region interaction effect) and (2) overall level (i.e., univariate main effect of Group). Given that adjusted z-scores re-express structural morphometric values as deviations from the HC expected value, profiles of z-scores for the HC group are flat (i.e., ROI means of zero), and NAff-P and Aff-P group profiles reflect deviations from HC norms.

First, in five separate Group (HC, NAff-P, Aff-P) × Hemisphere (Left, Right) × ROI rmMANOVA analyzing each morphometric ROI profile type (cortical thickness, cortical surface area, basal ganglia volume, subcortical volume, ventricular volume), we tested whether there was a significant three-way Group × Hemisphere × ROI interaction. For nonsignificant three-way interactions involving hemisphere, we averaged corresponding unilateral ROIs into bilateral ROIs. The only model with a significant three-way interaction was our basal ganglia model (caudate, putamen, pallidum; $P = .019$); therefore, we used unilateral ROIs and retained the hemisphere factor in this model only. Final ROIs included 34 bilateral cortical ROIs, 6 unilateral basal ganglia ROIs (left/right caudate, putamen, pallidum), 4 bilateral subcortical ROIs (accumbens, hippocampus, amygdala, thalamus), and 3 bilateral ventricular ROIs (lateral, inferior lateral, third ventricle).

Using our final ROIs and three groups (HC, NAff-P, Aff-P), we tested whether there was a significant two-way interaction of Group × ROI (i.e., nonparallelism) and a significant Group effect (i.e., level difference). Significant nonparallelism was followed-up with two-group Group × ROI rmANOVAs comparing profiles between each pair of groups. Last, following-up on significant nonparallelism of two-group rmANOVAs, we examined Bonferroni-corrected simple effects for each ROI.

When rmANOVAs were run to compare the subgroup of NAff-P patients with schizophrenia ($n = 58$) to the subgroup of Aff-P patients with bipolar disorder ($n = 24$), the results were essentially the same as those observed when the more heterogeneous NAff-P and Aff-P groups were compared (supplemental results).

Illness Duration and Antipsychotic Duration Analyses

To account for illness duration and antipsychotic duration, we separately included these variables as covariates in

our rmANCOVAs comparing NAff-P and Aff-P groups. To satisfy rmANCOVA assumptions, we first tested the three-way Group × ROI × Covariate interaction to ensure the groups did not show significant regression line slopes differences, subsequently dropping nonsignificant three-way interaction terms and proceeding with the rmANCOVA when not significant.

Chlorpromazine Equivalents, Lithium, and Clinical Measures Analyses

We next examined associations between structural morphometry with chlorpromazine equivalents, lithium, and clinical measures (clinical symptom severity, functioning, cognition). We used principal components analysis (PCA) with Promax rotation to reduce our ROIs to a smaller set of regional components. A separate PCA was run on unilateral ROIs for each morphometric measure in the combined sample. For full details on extracted components, see supplemental methods, supplementary tables 4–7, supplementary figures 1 and 2.

As only four Aff-P participants were currently taking antipsychotic medication, we examined Pearson correlations between the structural morphometry components and antipsychotic dosage (i.e., chlorpromazine equivalents) in the NAff-P group alone.

Additionally, as only a small number of early psychosis participants (NAff-P: $n = 6$; Aff-P: $n = 7$) were prescribed lithium, we did not include lithium as a covariate. However, since the seven participants represented 23.33% of Aff-P participants, we examined whether Aff-P lithium participants ($n = 7$) differed from Aff-P nonlithium participants ($n = 23$) on structural morphometry components. Due to the small and unbalanced groups in this analysis, we used non-parametric Mann–Whitney U tests to examine group differences.

For other clinical measures, we used general linear models to examine the Group × Clinical Measure interaction in NAff-P and Aff-P groups. When the interaction was not significant, it was dropped from the model, providing a test of the common slope across groups as well as a test of the Group effect on the brain component score while covarying for the clinical measure. Multiple comparisons within each morphometric measure were accounted for using false discovery rate (FDR) correction, $P_{FDR} < .05$.

Results

Participant Demographics

See table 1 for group demographics. Gender significantly differed between the groups ($P < .001$), reflecting more females in the Aff-P group but male predominance in the NAff-P and HC groups. Groups also significantly differed on age ($P < .001$), with NAff-P being slightly younger than HC ($P < .001$), but not Aff-P ($P = .127$).

Early psychosis groups did not significantly differ on illness duration ($t[107] = 0.24$, $P = .627$) or antipsychotic duration ($t[92] = 1.09$, $P = .277$). Significantly more NAff-P participants were currently prescribed chlorpromazine equivalents dosage ($\chi^2[2, N = 111] = 13.11$, $P < .001$), with only four Aff-P participants currently taking antipsychotic medication. Additionally, more Aff-P than NAff-P participants were taking lithium ($\chi^2[2, N = 113] = 5.61$, $P = .039$) and mood stabilizers ($\chi^2[2, N = 113] = 13.95$, $P < .001$). Antidepressant and anxiolytic medication use (all $P > .188$) as well as prevalence of current cannabis use disorders ($P = .089$) did not differ between the groups.

Cortical Thickness

Cortical thickness ROI z-score profiles (figure 1 and supplementary table 1) showed significant profile nonparallelism ($F[66,268] = 1.79$, Wilks' $\lambda = 0.48$, $P < .001$, $\eta_p^2 = 0.31$) and level differences ($F[2,166] = 21.51$, $P < .001$, $\eta_p^2 = 0.21$). In two-group follow-up comparisons with the HC profile, both NAff-P and Aff-P ROI profiles significantly deviated from the flat z-score HC profile (NAff-P: $F[33,105] = 2.53$, Wilks' $\lambda = 0.56$, $P < .001$, $\eta_p^2 = 0.44$; Aff-P: $F[33,52] = 1.67$, Wilks' $\lambda = 0.49$, $P = .048$, $\eta_p^2 = 0.51$). Additionally, the NAff-P group showed an overall reduction in profile level ($F[1,137] = 38.64$, $P < .001$, $\eta_p^2 = 0.22$), but not Aff-P group ($P = .238$). Relative to HC, the NAff-P group showed a reduction in cortical thickness across most ROIs, with some ROIs showing more prominent cortical thinning (insula, inferior parietal lobe, supramarginal gyrus, most of the temporal lobe regions) and two ROIs showing no thinning (entorhinal cortex, temporal pole; see figure 1 and supplementary table 1). Relative to HC, the Aff-P group showed a reduction in cortical thickness for the pars opercularis, rostral anterior cingulate, and middle temporal ROIs. Direct comparison of NAff-P and Aff-P groups showed their ROI profiles to be parallel ($F[33,79] = 1.34$, Wilks' $\lambda = 0.64$, $P = .147$, $\eta_p^2 = 0.36$) but with a significant level difference ($F[1,111] = 13.35$, $P < .001$, $\eta_p^2 = 0.11$), with the NAff-P group having a thinner cortex.

Cortical Surface Area

Cortical surface area ROI profiles across three groups showed significant nonparallelism ($F[66,268] = 2.11$, Wilks' $\lambda = 0.43$, $P < .001$, $\eta_p^2 = 0.34$) but no significant level difference ($F[2,166] = 1.08$, $P = .342$, $\eta_p^2 = 0.01$; figure 2 and supplementary table 2). In pairwise follow-up comparisons with the HC profile, both NAff-P and Aff-P profiles showed significant nonparallelism (NAff-P: $F[33,105] = 2.40$, Wilks' $\lambda = 0.57$, $P < .001$, $\eta_p^2 = 0.43$; Aff-P: ($F[33,52] = 2.18$, Wilks' $\lambda = 0.42$, $P = .006$, $\eta_p^2 = 0.58$) but no significant level differences (NAff-P: $F[1,137] = 0.90$, $P = .343$, $\eta_p^2 = 0.01$; Aff-P: $F[1,84] = 0.44$, $P = .509$, $\eta_p^2 = 0.01$). Relative to the

Table 1. Demographic Characteristics of Participant Groups.

	Mean ± SD			2-Group Comparison P		
	HC	NAff-P	Aff-P	HC v. NAff-P	HC v. Aff-P	NAff-P v. Aff-P
Gender (% male)[a]	66.07	72.29	30.00	–	–	–
Age (Range: 16–36)[b]	24.90 ± 4.08	22.38 ± 3.39	24.04 ± 4.39	< 0.001	.582	.105
Ethnicity Hispanic/Latino (%)[c]	16.07	7.23	6.67	–	–	–
Race (%)[d]						
White/Caucasian	71.43	39.75	76.67	–	–	–
Asian American	14.29	9.64	6.67	–	–	–
Black/African American	8.93	46.99	13.33	–	–	–
American Indian/Alaska Native	0.00	0.00	3.33	–	–	–
More Than One Race	1.79	1.20	0.00	–	–	–
Not Reported	3.57	2.41	0.00	–	–	–
Illness Duration (months)	–	20.56 ± 15.97	22.31 ± 18.18	–	–	.627
Medication and Substance Use						
Antipsychotic (%)	–	87.95	75.00	–	–	.043
Antipsychotic Duration (months)	–	17.86 ± 15.32	13.63 ± 16.77	–	–	.277
Chlorpromazine Equivalent (mg)[e]	–	230.82 ± 247.72	61.90 ± 149.92	–	–	–
Stimulant (%)[f]	–	2.41	3.33	–	–	–
Antidepressant (%)	–	28.92	16.67	–	–	.188
Anxiolytic (%)	–	22.89	16.67	–	–	.475
Lithium (%)	–	7.22	23.33	–	–	.039
Other Mood Stabilizers (%)	–	9.64	40.00	–	–	<.001
Alcohol Use Disorder (%)[f]	–	2.41	13.33	–	–	–
Cannabis Use Disorder (%)	–	8.43	20.00	–	–	.089

Note: HC, healthy control; NAff-P, nonaffective psychosis; Aff-P, affective psychosis.
[a]Groups were significantly different on gender (χ^2[2, N = 169] = 17.26, P < .001).
[b]Groups were significantly different on age, (F[2,166] = 7.64, P < .001), with NAff-P younger than HC (P < .001) and Aff-P (P = .105).
[c]Groups were not significantly different on ethnicity (χ^2[2, N = 169] = 3.35, P = .187).
[d]Groups were significantly different on race (χ^2[2, N = 169] = 31.07, P < .001).
[e]Significantly more NAff-P participants were currently prescribed chlorpromazine equivalents dosage (χ^2[2, N = 111] = 13.11, P < .001).
(χ^2[2, N = 169] = 31.07, P < .001).
[f]Group comparisons were not computed because of an n < 5 in at least one of the groups.

Table 2. Chlorpromazine Equivalents (CPZ) Pearson Correlations with Morphometric Principal Components in Non-Affective Psychosis (NAff-P).

Regional Factor	r	P
Thickness		
Temporal	−.23	.034
Frontal-Parietal	−.14	.216
Frontal	−.29	.003
Cingulate	−.06	.588
Temporal	−.08	.482
Surface Area		
Occipital	.12	.299
Frontal-Cingulate	.09	.419
Parietal	.00	.970
Middle Temporal	.11	.400
Superior Temporal	.02	.880
Frontal 1	.02	.881
Inferior Temporal 1	−.10	.386
Frontal 2	.09	.409
Inferior Temporal 2	.21	.056
Subcortical		
Basal Ganglia	.31	.004
Other Subcortical	−.06	.597
Ventricles		
All Ventricles	.16	.004

flat HC profile, the NAff-P profile showed prominent surface area increases in frontal, anterior cingulate, and superior temporal ROIs, and reductions in inferior temporal and paracentral gyrus ROIs. In contrast, relative to HC, the Aff-P profile showed prominent surface area increases in orbitofrontal and transverse temporal ROIs, and reductions in temporal gyri and parietal lobe ROIs. Direct comparison of NAff-P and Aff-P group profiles showed significant nonparallelism (F[33,79] = 2.34, Wilks' λ = 0.51, P = .001, η_p^2 = 0.49) but no level difference (F[1,111] = 1.55, P = .217, η_p^2 = 0.01; supplementary table 2), with the NAff-P profile showing relatively greater cortical surface area for superior and middle frontal lobe and anterior cingulate (caudal, isthmus) ROIs, and the Aff-P profile showing relatively greater increases in transverse temporal lobe and decreases in superior and middle temporal, orbital-frontal, sensorimotor (pre- and post-central gyrus), inferior parietal ROIs.

Basal Ganglia Volume (Caudate, Putamen, Pallidum)

Basal ganglia ROI profiles (caudate, putamen, pallidum) (figure 3a, supplementary table 3 and supplementary figure 3) showed a significant three-way
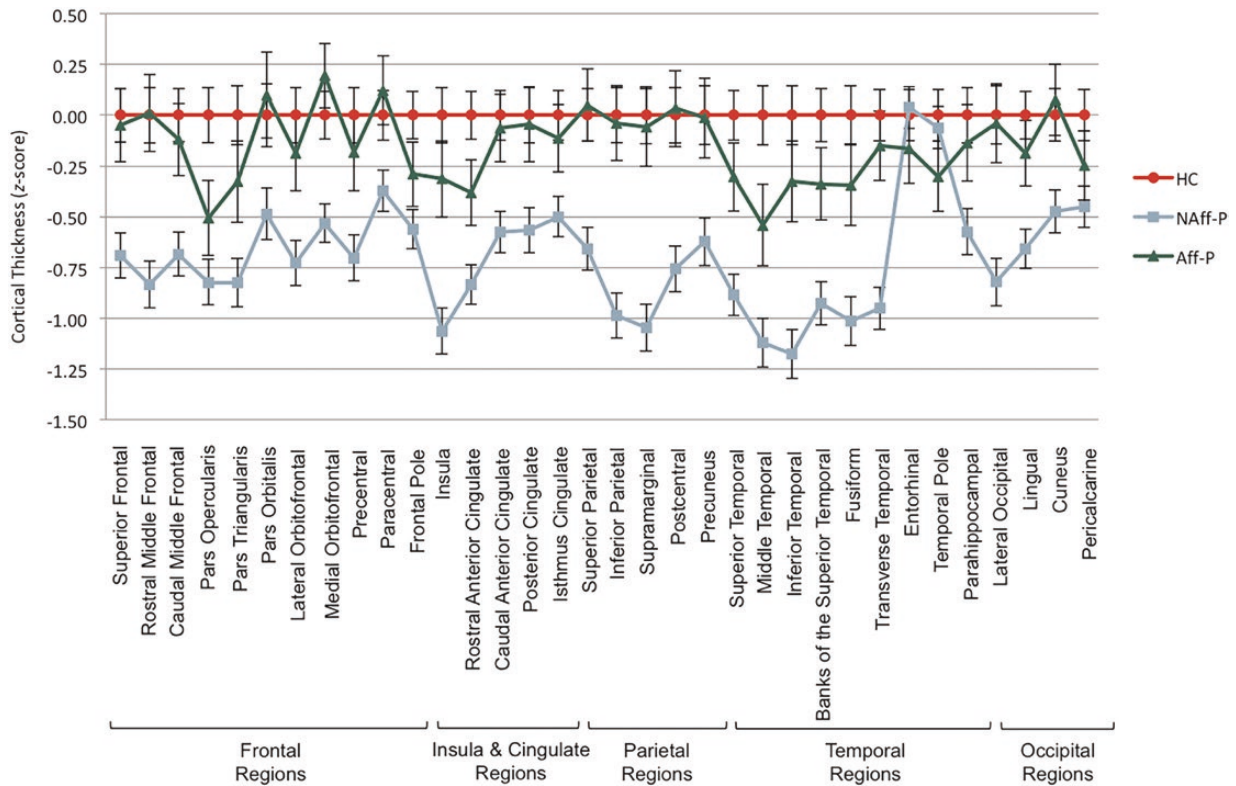
Fig. 1. Cortical thickness profiles of healthy control (HC), nonaffective psychosis (NAff-P) and affective psychosis (Aff-P) groups.
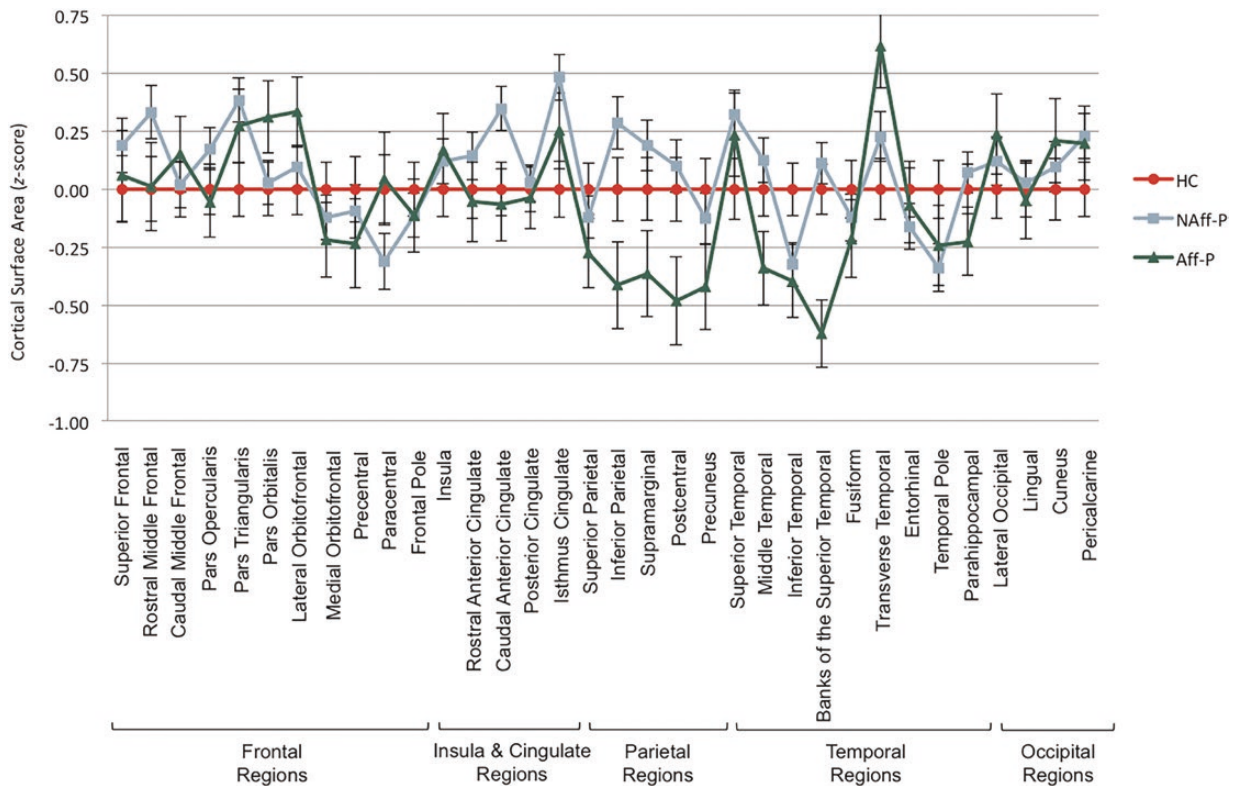

Fig. 2. Cortical surface area profiles of healthy control (HC), nonaffective psychosis (NAff-P), and affective psychosis (Aff-P) groups.
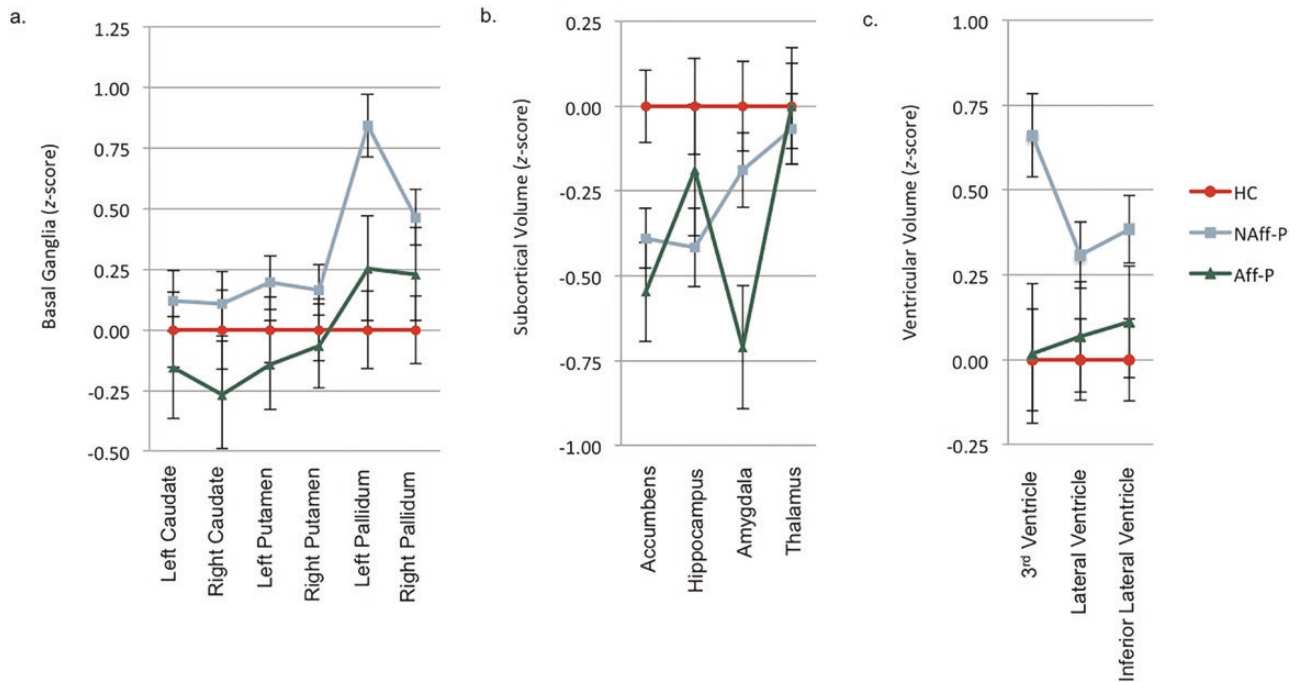
Fig. 3. Subcortical and ventricular volume profiles of healthy control (HC), nonaffective psychosis (NAff-P), and affective psychosis (Aff-P) groups.

Group × ROI × Hemisphere interaction ($F[4,330] = 3.01$, Wilks' $\lambda = 0.93$, $P = .019$, $\eta_p^2 = 0.04$). To parse this interaction, two-way Group × ROI rmANOVA models were run separately by hemisphere. Results showed significant profile nonparallelism ($F[4,330] = 3.07$, Wilks' $\lambda = 0.93$, $P = .017$, $\eta_p^2 = 0.04$) and left hemisphere level differences ($F[2,166] = 4.24$, $P = .016$, $\eta_p^2 = 0.05$), but not the right hemisphere ($P > .157$, $\eta_p^2 < 0.022$). In a two-group follow-up analyses of left hemisphere ROI profiles, HC and NAff-P profiles showed significant nonparallelism ($F[2,136] = 6.07$, Wilks' $\lambda = 0.92$, $P = .003$, $\eta_p^2 = 0.08$), with the NAff-P group having a significantly enlarged left pallidum ($P < .001$), but only slight and non-significant ($P > .275$) enlargement of caudate and putamen, relative to the HC's flat z-score profile. This pallidum enlargement, when averaged with caudate and putamen ROIs, was large enough to drive a significant overall profile level elevation in the NAff-P group ($F[1,137] = 6.31$, $P = .013$, $\eta_p^2 = 0.04$). There were no significant profile parallelism or level differences between HC and Aff-P groups ($P > .154$, $\eta_p^2 = 0.00$ to 0.04). Between NAff-P and Aff-P groups, there was no significant profile difference ($P = .554$, $\eta_p^2 = 0.01$), but the NAff-P group showed overall greater basal ganglia volume ($F[1,111] = 4.00$, $P = .048$, $\eta_p^2 = 0.04$).

Subcortical Volume (Accumbens, Hippocampus, Amygdala, Thalamus)

Comparison of subcortical ROI (accumbens, hippocampus, amygdala, thalamus) volume profiles between

groups (figure 3b and supplementary table 3) indicated significant profile nonparallelism ($F[6,328] = 3.01$, Wilks' $\lambda = 0.90$, $P = .007$, $\eta_p^2 = 0.05$) and level differences ($F[2,166] = 3.68$, $P = .027$, $\eta_p^2 = 0.04$) that did not significantly interact with hemisphere ($P = .084$). In two-group follow-up comparisons, the NAff-P profile was parallel with the flat HC profile ($F[3,135] = 1.87$, Wilks' $\lambda = 0.96$, $P = .138$, $\eta_p^2 = 0.04$), but showed a significant overall level reduction ($F[1,137] = 5.10$, $P = .026$, $\eta_p^2 = 0.04$) indicating smaller subcortical volumes in NAff-P (supplementary table 3). Comparing HC and Aff-P, the Aff-P profile was significantly nonparallel ($F[3,82] = 3.19$, Wilks' $\lambda = 0.90$, $P = .028$, $\eta_p^2 = 0.10$) with the flat HC profile, reflecting relatively smaller accumbens ($P = .006$) and amygdala ($P = .002$) but normal hippocampus and thalamus volumes ($P > .399$; supplementary table 3). These subcortical ROI volume deficits drove an overall profile level reduction in the Aff-P group ($F[1,84] = 6.57$, $P = .012$, $\eta_p^2 = 0.07$). In the NAff-P and Aff-P comparison, there was significant profile nonparallelism ($F[3,109] = 3.94$, Wilks' $\lambda = 0.94$, $P = .010$, $\eta_p^2 = 0.10$), driven mainly by a relatively smaller amygdala volume in Aff-P than NAff-P ($P = .020$; supplementary table 3). The Aff-P and NAff-P subcortical volume profiles did not differ in overall level ($F[1,111] = 0.41$, $P = .525$, $\eta_p^2 = 0.00$).

Ventricular Volume

For ventricular ROIs (figure 3c and supplementary table 3), there was no significant group nonparallelism

Table 3. Clinical Measures (Beta Values) with Cortical Thickness Components in Early Psychosis.

Regional Factor[a]	PANSS Positive	PANSS Negative	PANSS Cognitive	CAINS Motivation	CAINS Expression	MADRS	YMRS	GAF Symptom	GAF Occupation	GAF Social	WASI Vocabulary	WASI Matrix
Temporal-Occipital												
1. Group	−0.35***	−0.36***	−0.34***	−0.36***	−0.35***	−0.33***	−0.36***	−0.37***	−0.34***	−0.35***	−0.35***	−0.34***
1. Covariate	−0.02	0.00	−0.08	0.11	−0.03	0.15	0.01	−0.17	−0.01	−0.05	0.05	0.09
Frontal-Parietal												
1. Group	−0.30**	−0.30**	−0.32**	0.17*	−0.27**	−0.29**	−0.31**	−0.30**	−0.28**	−1.13**	−0.31**	−0.29**
1. Covariate	−0.02	−0.03	0.04	0.45*	−0.06	0.08	−0.10	−0.02	0.08	−0.299	−0.04	0.04
2. Group × Covariate	—	—	—	−0.63*	—	—	—	—	—	0.87*	—	—
NAff-P Slope	—	—	—	−0.05	—	—	—	—	—	0.11	—	—
Aff-P Slope	—	—	—	0.51**	—	—	—	—	—	−0.38*	—	—
Frontal												
1. Group	−0.32**	−0.28**	−0.28**	−0.28**	−0.27**	−0.26**	−0.28**	−0.27**	−0.24*	−1.25**	−0.31**	−0.31**
1. Covariate	0.08	−0.01	−0.01	0.15	−0.01	0.11	0.10	−0.06	0.08	−0.30	−0.09	0.01
2. Group × Covariate	—	—	—	—	—	—	—	—	—	1.03*	—	—
NAff-P Slope	—	—	—	—	—	—	—	—	—	0.17	—	—
Aff-P Slope	—	—	—	—	—	—	—	—	—	−0.38*	—	—
Cingulate												
1. Group	−0.31**	−0.30**	−0.32**	−0.28**	−0.27**	−0.28**	−0.28**	−0.28**	−0.28**	−0.30**	−0.34***	−0.56***
1. Covariate	0.05	0.04	0.10	0.02	−0.01	0.08	0.17	0.17	0.03	0.02	−0.09	0.00
Temporal												
1. Group	−0.62*	−0.02	−0.01	0.01	0.01	−0.03	−0.03	−0.01	−0.01	0.00	−0.03	−0.03
1. Covariate	−0.63*	0.03	0.00	−0.05	0.00	−0.04	−0.14	0.03	−0.05	0.08	0.02	−0.01
2. Group × Covariate	1.04*	—	—	—	—	—	—	—	—	—	—	—
NAff-P Slope	0.03	—	—	—	—	—	—	—	—	—	—	—
Aff-P Slope	−0.49**	—	—	—	—	—	—	—	—	—	—	—

Note: PANSS, Positive and Negative Symptom Scale; CAINS, Clinical Assessment Interview for Negative Symptoms; MADRS, Montgomery–Asberg Depression Rating Scale; YMRS, Young Mania Rating Scale; GAF, Global Assessment of Functioning; WASI, Wechsler Abbreviate Scale Intelligence. Group × Covariate and group slopes were not reported when interaction was not significant. None of the Group × Covariate interactions were significant for temporal-occipital and cingulate measures.

[a]The 1 and 2 before each predictor denotes the step in the model in which the predictor was entered.

*P < .05 prior to FDR correction.

**P < .01 prior to FDR correction.

***P < .001 prior to FDR correction.

(F[4,330] = 1.66, Wilks' λ = 0.96, P = .158, η_p^2 = 0.02). However, group profiles showed significant level differences (F[2,166] = 6.48, P = .002, η_p^2 = 0.07), with post hoc tests indicating ventricular enlargement in NAff-P relative to HC (P = .003) and Aff-P (P = .055) groups, which did not differ from each other (P = .926).

Illness Duration and Antipsychotic Duration

Profile results accounting for illness duration and antipsychotic duration in NAff-P and Aff-P showed the same pattern of results with regard to the above parallelism and level results (except for loss of the previously significant group differences in basal ganglia profile levels; supplemental results; supplementary figure 4).

Chlorpromazine Equivalents and Lithium

With regard to chlorpromazine equivalents dosage in the NAff-P group (table 2), greater chlorpromazine equivalents was associated with less temporal-occipital (r = −0.23, P = .034) and frontal thickness (r = −0.29, P = .003) as well as increased basal ganglia volume (r = 0.31, P = .004). Chlorpromazine equivalents was not significantly associated with surface area (all P > .056), other subcortical regions (P = .597), or ventricular volume (P = .163) components.

To account for potential effects of lithium, we ran additional analyses comparing Aff-P participants prescribed lithium and Aff-P participants who were not prescribed lithium. Aff-P lithium and nonlithium participants did not significantly differ on cortical thickness (all P > .311), cortical surface area (all P > .190), basal ganglia volume (P = .335), other subcortical volume (P = .774), or ventricular volume (P = .886) components.

Clinical Measures

The NAff-P group had significantly greater PANSS Positive (t[106] = 5.13, P < .001), PANSS Negative (t[106] = 3.13, P = .002), PANSS Cognitive (t[106] = 3.14, P = .002), and CAINS Expression (t[103] = 4.00, P < .001), as well as significantly lower MADRS scores (t[107]=−2.02, P = .046) than the Aff-P group (supplementary table 8). The two groups did not significantly differ on CAINS Motivation, or YMRS (all P > .864).

There were significant differences among all three groups for functioning and cognition (all P < .001, supplementary table 8). Specifically, NAff-P had functioning and cognitive deficits compared to HC (all P < .001), whereas Aff-P only showed functioning deficits (all P < .001). Furthermore, NAff-P had cognitive deficits (all P < .050) compared to Aff-P.

In examining associations between our morphometric components and these clinical measures in the NAff-P and Aff-P groups (tables 3–5), there was one association

that survived FDR correction. Specifically, greater ventricular volume in early psychosis, that did not interact with group, was associated with increased manic symptoms (F[1,106] = 8.61, β = 0.040, P = .004; table 4).

Discussion

Morphometric brain abnormalities have been reported in NAff-P[1–8] and Aff-P across the illness course,[5–7,9–14] with evidence for both common and distinct profiles of abnormalities.[10,14–17] However, illness chronicity and prolonged medication exposure can confound this relationship in chronic populations.[5,6,13] Hence, the current study focused on brain morphometry of early psychosis NAff-P and Aff-P samples. Consistent with our hypotheses and prior studies, participants with early psychosis had brain morphometric abnormalities relative to HC, with more pronounced and widespread abnormalities in NAff-P than Aff-P. Moreover, direct comparison of NAff-P and Aff-P groups revealed differences in overall level of abnormalities and/or the pattern of their regional profiles, depending on the type of morphometric measure (i.e., thickness, surface area, volume) and whether cortical or subcortical regions were considered. Despite these group differences, which largely reflect differential manifestations of structural brain abnormalities in the early course of schizophrenia spectrum disorders versus bipolar and unipolar affective disorders, clinical and cognitive measures were not significantly associated with structural morphometric measures within either group. Thus, results suggest that distinct underlying pathophysiological processes in schizophrenia spectrum and mood spectrum psychoses give rise to different levels and nonparallel profiles of brain dysmorphologies in early psychosis.

Specifically, NAff-P had widespread cortical thinning compared to HC and Aff-P, with significant profile differences between HC and Aff-P. Previous research has consistently found cortical thinning in both chronic schizophrenia[3,5,14,83] and early illness NAff-P compared to HC.[19–26] Although we did not find significant overall cortical thinning in Aff-P compared to HC, there was significant thinning in pars opercularis, rostral anterior cingulate, and middle temporal ROIs and some nonsignificant increases in thickness of some ROIs. Previous research has shown modest cortical thinning in chronic bipolar disorder[13,14,83] and early illness Aff-P patients[24,27] (and some evidence of increased cortical thickness[26]) that is less pronounced than the thinning in NAff-P patients, which is particularly prominent in frontotemporal regions.[24–27] Thus, our results are generally consistent with prior research showing greater cortical thinning in early illness NAff-P relative to Aff-P.

In contrast to cortical thickness, cortical surface area has been less studied. Chronic schizophrenia has shown evidence of reduced cortical surface area,[5,14]

Table 4. Clinical Measures (Beta Values) with Cortical Surface Area Components in Early Psychosis.

Regional Factor[a]	PANSS Positive	PANSS Negative	PANSS Cognitive	CAINS Motivation	CAINS Expression	MADRS	YMRS	GAF Symptom	GAF Occupation	GAF Social	WASI Vocabulary	WASI Matrix
Occipital												
1. Group	0.07	−0.02	−0.03	−0.02	0.01	−0.06	−0.03	0.00	0.02	−0.01	−0.01	−0.01
1. Covariate	−0.21	0.00	0.03	−0.25*	−0.01	−0.17	−0.22*	0.18	0.12	0.18	0.04	0.05
Frontal-Cingulate												
1. Group	0.10	0.07	0.08	0.05	0.05	0.05	0.05	0.05	0.08	0.04	0.09	0.06
1. Covariate	−0.13	−0.07	−0.12	−0.02	−0.01	0.01	0.05	−0.03	0.07	−0.05	0.16	−0.03
Parietal												
1. Group	0.15	0.13	0.13	0.14	0.16	0.15	0.14	0.14	0.17	0.15	0.18	0.14
1. Covariate	−0.04	0.00	0.02	−0.07	−0.07	0.05	0.07	0.00	0.08	0.05	0.11	−0.11
Middle Temporal												
1. Group	0.26*	0.27**	0.26**	0.33***	0.30**	0.28**	0.29**	0.33***	0.35***	0.31**	0.33***	0.32***
1. Covariate	0.09	0.07	0.10	−0.04	0.08	−0.06	−0.12	0.05	0.05	−0.13	0.00	−0.02
Superior Temporal												
1. Group	0.06	0.04	0.08	0.04	0.01	0.06	0.04	0.04	0.03	0.04	0.09	0.05
1. Covariate	−0.02	0.03	−0.11	−0.01	0.07	0.10	0.10	−0.02	0.01	−0.03	0.20*	0.00
Frontal 1												
1. Group	−0.03	−0.03	−0.01	−0.04	−0.03	−0.04	−0.06	−0.05	−0.04	2.00*	−0.02	−0.06
1. Covariate	−0.05	−0.09	−0.13	−0.04	−0.05	0.10	0.00	0.00	0.02	1.85	0.23*	0.07
2. Group × Covariate	—	—	—	—	—	—	—	—	—	−2.17*	—	—
NAff-P Slope	—	—	—	—	—	—	—	—	—	−0.12	—	—
Aff-P Slope	—	—	—	—	—	—	—	—	—	0.38*	—	—
Inferior Temporal 1												
1. Group	0.04	−0.02	0.04	−0.01	−0.06	−0.24	−0.03	−0.01	−0.04	−0.02	0.05	0.02
1. Covariate	−0.13	0.00	−0.21*	0.11	0.14	−0.31*	−0.08	0.05	0.02	−0.02	0.27**	0.17
2. Group × Covariate	—	—	—	—	—	0.36*	—	—	—	—	—	—
NAff-P Slope	—	—	—	—	—	0.10	—	—	—	—	—	—
Aff-P Slope	—	—	—	—	—	−0.37	—	—	—	—	—	—
Frontal 2												
1. Group	0.04	0.11	0.06	0.12	0.14	0.11	0.08	0.10	0.11	0.09	0.11	0.10
1. Covariate	0.09	−0.08	0.06	−0.01	−0.06	0.19*	−0.01	0.01	−0.01	−0.11	0.06	0.05
Inferior Temporal 2												
1. Group	0.06	0.08	0.05	0.14	−0.10	0.13	0.13	0.15	0.16	1.01*	0.11	0.13
1. Covariate	0.18	0.20	0.29**	0.19	−0.36*	0.01	−0.05	−0.11	−0.06	0.16	−0.20*	−0.07
2. Group × Covariate	—	—	—	—	0.69*	—	—	—	—	−0.90*	—	—
NAff-P Slope	—	—	—	—	0.33**	—	—	—	—	−0.26*	—	—
Aff-P Slope	—	—	—	—	−0.24	—	—	—	—	0.17	—	—

Note: PANSS, Positive and Negative Symptom Scale; CAINS, Clinical Assessment Interview for Negative Symptoms; MADRS, Montgomery-Asberg Depression Rating Scale; YMRS, Young Mania Rating Scale; GAF, Global Assessment of Functioning; WASI, Wechsler Abbreviate Scale Intelligence. Group × Covariate and group slopes were not reported when interaction was not significant. None of the Group × Covariate interactions were significant for occipital, frontal-cingulate, parietal, middle temporal, superior temporal, and frontal 2 measures.

[a]The 1 and 2 before each predictor denotes the step in the model in which the predictor was entered.

*P < .05 prior to FDR correction.

**P < .01 prior to FDR correction.

***P < .001 prior to FDR correction.

Table 5. Clinical Measures (Beta Values) with Subcortical and Ventricular Volume Components in Early Psychosis.

Regional Factor[a]	PANSS Positive	PANSS Negative	PANSS Cognitive	CAINS Motivation	CAINS Expression	MADRS	YMRS	GAF Symptom	GAF Occupation	GAF Social	WASI Vocabulary	WASI Matrix
Basal Ganglia												
1. Group	0.08	0.10	0.10	0.54*	0.08	0.11	0.12	0.17	0.17	0.14	0.12	0.13
1. Covariate	0.09	0.06	0.06	0.40*	0.11	-0.05	-0.10	0.15	0.15	-0.06	-0.04	-0.05
2. Group × Covariate	–	–	–	-0.58*	–	–	–	–	–	–	–	–
NAff-P Slope	–	–	–	-0.06	–	–	–	–	–	–	–	–
Aff-P Slope	–	–	–	0.44*	–	–	–	–	–	–	–	–
Other Subcortical												
1. Group	0.03	0.04	0.08	0.47*	0.05	0.08	0.05	0.02	0.06	0.03	0.08	0.10
1. Covariate	0.04	0.05	-0.09	0.41*	0.04	0.11	-0.05	-0.11	0.08	-0.02	0.14	0.23*
2. Group × Covariate	–	–	–	-0.55*	–	–	–	–	–	–	–	–
NAff-P Slope	–	–	–	-0.03	–	–	–	–	–	–	–	–
Aff-P Slope	–	–	–	0.42*	–	–	–	–	–	–	–	–
Ventricles												
1. Group	0.12	0.17	0.20	0.15	0.14	0.15	0.18	0.15	0.18	0.16	0.17	0.14
1. Covariate	0.12	-0.02	-0.09	0.06	0.03	-0.09	**0.27****	-0.14	-0.06	-0.09	0.01	-0.19*

Note: Bolded text denotes test that survived FDR correction. PANSS, Positive and Negative Symptom Scale; CAINS, Clinical Assessment Interview for Negative Symptoms; MADRS, Montgomery-Asberg Depression Rating Scale; YMRS, Young Mania Rating Scale; GAF, Global Assessment of Functioning; WASI, Wechsler Abbreviate Scale Intelligence. Group × Covariate and Group slopes were not reported when interaction was not significant. None of the Group × Covariate interactions were significant for ventricular measures.

[a]The 1 and 2 before each predictor denotes the step in the model in which the predictor was entered.

*P < .05 prior to FDR correction.
**P < .01 prior to FDR correction.
***P < .001 prior to FDR correction.

whereas evidence of surface area abnormalities in bipolar disorder is limited.[13] In early psychosis, studies have not reported significant deficits.[21,28] In the current study, cortical surface area regional profiles did not differ in overall level, consistent with prior studies. However, relative to the flat HC z-score profile, both early psychosis group profiles were significantly and distinctly nonparallel, suggesting group-specific regional patterns of abnormalities. In particular, in NAff-P, abnormal cortical surface area regions were significant in frontotemporal regions. In contrast, Aff-P showed a different pattern of abnormalities in frontal (increased orbital frontal) and temporal/parietal (increased transverse temporal; reduced temporal gyri and parietal lobe) regions. Finally, some surface area abnormalities were particularly prominent in distinguishing NAff-P and Aff-P groups, with NAff-P showing relatively larger superior/middle frontal and anterior cingulate regions, and the Aff-P showing relatively larger transverse temporal, but smaller superior/middle temporal, orbitofrontal, sensorimotor, and inferior parietal regions. Frontal and anterior cingulate regions are crucial for integrating cognitive and emotional processes in supporting goal-directed behavior.[84,85] Abnormalities of these regions are thought to underlie difficulties in cognitive-emotional integration in NAff-P.[86,87] Additionally, sensorimotor and inferior parietal lobe regions are involved in sensorimotor integration of the mirror neuron system[88] and language tasks.[89] The temporal lobe receives projections from the amygdala and is hypothesized to relay visual perceptions into the emotion processing circuit.[90] As such, structural deficits in these regions may be implicated in emotion perception deficits and fluctuating mood states associated with Aff-P.[91,92] These distinct patterns in NAff-P and Aff-P highlight the importance of examining parallelism and level of ROI profiles to characterize their shared and distinguishing features. As there have only been a few surface area studies published till date, future replication studies are needed given limited abnormalities in chronic illness stages[13,14] and normal surface areas reported in early psychosis.[21,28]

Arguably, the most distinct brain morphometry differences between NAff-P and Aff-P emerging from prior chronic and early psychosis studies have been for subcortical and ventricular volumes. NAff-P has been characterized by reduced hippocampal,[6,7,27,29–31,93] enlarged caudate volumes,[32] and enlarged ventricles.[6,33,34,52,93–95] In contrast, lithium-naïve/unmedicated Aff-P has been characterized by smaller amygdala volumes.[37,39,40] Current study results showed a similar pattern. The NAff-P subcortical ROI profile showed an overall level reduction compared to HC, but a trend toward nonparallelism highlighted that deficits were in hippocampal and accumbens ROIs. The basal ganglia profile for NAff-P was significantly nonparallel to the flat HC profile, an effect largely driven by left pallidum enlargement, and

showed greater overall volume relative to the Aff-P group. Previous research has found increased basal ganglia volumes in schizophrenia,[96,97] including a left-lateralized increase in pallidum volume[2] similar to current findings, an effect attributed to antipsychotic medication exposure.[81,98,99] The Aff-P subcortical profile was significantly nonparallel to the flat HC profile and the distinct NAff-P profile, driven mainly by reduced accumbens volume relative to HC and reduced amygdala volume relative to both HC and NAff-P groups. The majority of the Aff-P group was not taking lithium, and this is consistent with previous research on lithium-naïve/unmedicated Aff-P individuals exhibiting reduced amygdala volumes relative to both HC.[37,39]

Ventricular volume profiles showed an abnormal level increase in NAff-P, but not in Aff-P. This is consistent with widespread ventricular enlargement observed across the course of schizophrenia,[6,93–95] including in first-episode patients,[26,33,34,52] and mixed evidence of ventricular enlargement in the early illness phase of Aff-P.[18,26,30] Overall, results highlight the potential of subcortical and ventricular volumes as biomarkers of distinct patterns of brain dysmorphology underlying NAff-P and Aff-P at illness onset.

As illness duration and medication have been found to be associated with brain morphometry, we further examined the relationship with these variables in our analyses. When accounting for illness duration and antipsychotic duration in the NAff-P and Aff-P groups, the general pattern of results remained the same (except for basal ganglia profiles). With regard to chlorpromazine dose equivalents in the NAff-P, higher doses were associated with more temporal-occipital and frontal cortical thinning as well as increased basal ganglia volume. Of note, this fronto-temporal pattern has been found in both antipsychotic-naïve and antipsychotic-treated individuals with NAff-P.[100–102] Moreover, cortical thinning in the current NAff-P group, relative to the Aff-P group, was not confined to the fronto-temporal cortical regions showing significant correlations with current CPZ dose, indicating that NAff-P cortical thickness deficits are widespread and unlikely to be exclusively the result of antipsychotic medication exposure. Additionally, consistent with our results, previous research has found increased antipsychotic dosage to be associated with enlarged caudate volumes.[81] To account for potential effects of lithium, we compared Aff-P participants prescribed lithium and Aff-P participants who were not prescribed lithium. Aff-P lithium and nonlithium participants did not significantly differ on brain morphometry. Note that this subgroup analysis was underpowered and previous research has found Aff-P lithium participants to have greater amygdala volume.[39,40]

Last, we examined clinical symptom severity, functioning, and cognition. Consistent with its predominant inclusion of patients with schizophrenia, the NAff-P

group had greater symptom severity on the PANSS and the CAINS Expression scale, fewer depressive symptoms, and worse cognition, than the Aff-P group. However, both showed poor functioning relative to HC, consistent with prior early psychosis studies.[41,42,44] Given prior mixed results examining associations of structural morphometry with symptom severity and functioning,[19,45,103–105] it was not surprising that only the association between mania and ventricular volume was significant. Previous research has found greater ventricular volume to be associated with higher number of manic episodes.[106] It is possible that stronger associations with other variables would be present in longitudinal studies.[20]

There are some limitations worth noting. One limitation was the relatively smaller sample of Aff-P compared to the other two groups. Another limitation was that traveling subjects data were not collected from all scanning sites for use as correction factors in harmonization protocols. However, as mentioned above, harmonization across sites was achieved through the use of identical scanners, scan sequences, and protocols. Scanning site variation was also statistically accounted for in our z-scoring adjustment procedure. Furthermore, this was a cross-sectional study, and future HCP-EP longitudinal releases should examine brain structure changes over time and if these changes are related to clinical outcomes. Additionally, although we attempted to statistically control for age and gender, groups were unbalanced on age, gender, and race. Last, while our study included patients within the first five years of illness onset, they were not first-episode psychosis patients; therefore, differences in the nonaffective and affective psychosis groups may have arisen, at least partially, from differences in their post-onset illness course and treatments. Accordingly, future studies are needed to replicate our results in a first-episode/unmedicated sample.

Overall, the current study showed that early psychosis morphological profiles had not only common but also different levels and patterns of brain dysmorphologies, suggesting the presence of distinct underlying pathophysiological processes in schizophrenia spectrum and mood spectrum psychoses. The similarity in the pattern of current early illness results to chronic psychosis research adds to the evidence[100] that much of the progression of structural morphometric changes is occurring in the first five years of psychosis, and the pattern evident in this early stage of psychosis resembles the patterns present in chronic stages, consistent with both a neurodevelopmental origin of these abnormalities and/or a progressive pathophysiological process affecting similar brain regions across the illness course. Knowledge of the shared patterns and differences between these two early psychosis groups could help in understanding underlying mechanisms and in identifying neurobiological markers to improve diagnostic accuracy and inform early psychosis intervention.

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