Archival Report

Biological Psychiatry

Regional and Sex-Specific Alterations in the Visual Cortex of Individuals With Psychosis Spectrum Disorders

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ABSTRACT

BACKGROUND: Impairments of the visual system are implicated in psychotic disorders. However, studies exploring visual cortex (VC) morphology in this population are limited. Using data from the Bipolar-Schizophrenia Network on Intermediate Phenotypes consortium, we examined VC structure in psychosis probands and their first-degree relatives (RELs), sex differences in VC measures, and their relationships with cognitive and peripheral inflammatory markers.

METHODS: Cortical thickness, surface area, and volume of the primary (Brodmann area 17/V1) and secondary (Brodmann area 18/V2) visual areas and the middle temporal (V5/MT) region were quantified using FreeSurfer version 6.0 in psychosis probands (n = 530), first-degree RELs (n = 544), and healthy control subjects (n = 323). Familiality estimates were determined for probands and RELs. General cognition, response inhibition, and emotion recognition functions were assessed. Systemic inflammation was measured in a subset of participants.

RESULTS: Psychosis probands demonstrated significant area, thickness, and volume reductions in V1, V2, and MT, and their first-degree RELs demonstrated area and volume reductions in MT compared with control subjects. There was a higher degree of familiality for VC area than thickness. Area and volume reductions in V1 and V2 were sex dependent, affecting only female probands in a regionally specific manner. Reductions in some VC regions were correlated with poor general cognition, worse response inhibition, and increased C-reactive protein levels.

CONCLUSIONS: The visual cortex is a site of significant pathology in psychotic disorders, with distinct patterns of area and thickness changes, sex-specific and regional effects, potential contributions to cognitive impairments, and association with C-reactive protein levels.

https://doi.org/10.1016/j.biopsych.2022.03.023

The visual system is an important site of pathology in psychotic disorders. Visual system impairments manifest as basic visual symptoms (1), visual perceptual deficits (2), and abnormalities in the structure (3) and functional activity (4) of visual brain areas. Studies have demonstrated impairments in multiple levels of visual processing streams, ranging from early visual cortex (VC) functions [e.g., contrast sensitivity (5), perceptual integration (6)] to extrastriate cortex [e.g., speed discrimination (7)] and higher-order visual functions [e.g., eye movements (8)], which are associated with negative (2) or positive (6) symptoms. In addition, early visual processing deficits may affect higher-order cognitive functions such as emotion recognition, via bottom-up mechanisms (9,10). Visual impairments are also demonstrated in first-degree relatives of individuals with psychosis (7,11) and healthy individuals with schizotypal features (12,13). Furthermore, visual function impairment in childhood and adolescence is linked to later development of schizophrenia (14,15). Thus, evidence suggests that impairments of the visual system are of significance in understanding psychosis pathophysiology and may have potential clinical applications.

Despite increasing interest in visual system impairments in psychosis, studies focusing on visual cortical structure are limited. Studies have identified reduced thickness and surface area in the occipital cortex in individuals with psychosis (16), including early course (17). VC subregions, which have distinct structures, functions, and development (18), are less explored in psychosis with mixed results. Thinning in the retinotopic cortex was demonstrated in psychosis but not in subregions (V1, V2, and V3) (19). Another study demonstrated cortical thinning in V5/middle temporal (MT)+ and V2 but not in V1 (3). Reductions in V1 volume are found in postmortem studies (20).

ISSN: 0006-3223

The regional specificity of these alterations remains a critical question given the widespread nature of cortical abnormalities in psychosis (21). It is also unclear to what extent these abnormalities represent intermediate phenotypes of psychosis risk. Despite the visual impairments observed in first-degree relatives (7,11), limited data exist on VC structural alterations.

Sexual dimorphism is a well-studied characteristic of the visual system, as demonstrated by behavioral, neurophysiological, and neuroimaging studies (22,23). Healthy females have lower surface area and volume in V1 and V2 than healthy males (24). Sex differences in clinical and biological characteristics of schizophrenia are also well established (25,26). There is a disrupted pattern of sexual dimorphic neuroanatomy in schizophrenia, which is likely modulated by sex steroid hormones and manifests as more pronounced sex differences in brain structure (25,27). Despite marked sexual dimorphism in the visual system (22,23), the effect of sex on visual cortical morphology in psychosis is unclear. Elucidating sex differences may inform disease mechanisms by uncovering developmental sex-related modifications in the phenotypic expression of schizophrenia.

VC structure is also influenced by systemic inflammation via brain microstructural and/or blood-brain barrier changes (28–30). Maternal inflammation studies have identified neuronal, morphological, and electrophysiological changes in the primary VC in exposed rodent offspring (29). In healthy individuals, systemic inflammation resulted in a rapid change in striate (V1) microstructure (30). Growing evidence suggests that peripheral inflammatory markers (e.g., interleukin [IL] 1β, IL-6, tumor necrosis factor α [TNF-α], and C-reactive protein [CRP]) are associated with both psychosis (31–33) and brain structural alterations (34), including an association between higher IL-6 and TNF-α with higher global free water levels, which suggests the presence of inflammation-mediated disruption of the blood-brain barrier (35–37). To our knowledge, no study to date has examined the relationship between inflammation and visual cortical structures in psychosis. Additional support for blood-brain barrier disruption in the VC comes from evidence of vascular degeneration of endothelial cells and astroglial processes in postmortem schizophrenia brains (38). Furthermore, visual cortical alterations may result from systemic inflammation as opposed to neuroinflammatory processes, which is supported by the absence of glial density differences (39,40) and reduced microglial and astrocytic activity (41) in the occipital cortex.

Herein, using a large multimodal dataset from the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP) consortium, we aimed to investigate area, thickness, and volume alterations in VC subregions (primary [Brodmann area (BA) 17/V1], secondary [BA 18/V2], and middle temporal [V5/MT] areas) in individuals with psychosis and their first-degree relatives (RELs) compared with healthy control (HC) subjects, their regional specificity, and sex-specific effects on these measures. Our secondary aims were to evaluate familiality of visual cortical measures and their correlation with clinical, cognitive, and peripheral inflammatory measures. We hypothesized that, compared with HC subjects, psychosis probands and RELs would demonstrate lower VC area, thickness, and volume, as well as a high degree of familiality. We predicted a more pronounced sexual dimorphism in the VC in female probands, which would result in greater area and volume reductions compared with male probands. We expected lower visual cortical measures to be associated with higher psychosis symptom severity, poorer cognition, and higher peripheral inflammation.

METHODS AND MATERIALS

Study Sample

B-SNIP participants with available brain imaging measures were included in the study. B-SNIP procedures, detailed elsewhere (42), were approved by Institutional Review Boards, and all participants provided informed consent. Participants were assessed using the Structured Clinical Interview for DSM-IV Axis I disorders (43). HC subjects and RELs were evaluated with the Structured Interview for DSM-IV Personality (44). A total of 530 probands with a diagnosis of schizophrenia, schizoaffective disorder, or bipolar I disorder with psychotic features, 544 RELs, and 323 HC subjects were included in the final analysis. RELs included clinically unaffected relatives with no lifetime Axis I or Axis II diagnoses (REL-U, n = 206) and relatives with lifetime psychiatric diagnoses. Symptom severity was assessed using the Positive and Negative Syndrome Scale (45), Young Mania Rating Scale (46), and Montgomery–Åsberg Depression Rating Scale (47). Global Assessment of Functioning (43) and the Birchwood Social Functioning Scale (48) were used to assess functioning. See Table 1 for demographic and clinical characteristics.

Cognition

The reading subtest of the Wide Range Achievement Test-4 (49) and the Brief Assessment of Cognition in Schizophrenia (BACS) (50) were administered to assess cognition. The antisaccade paradigm evaluated inhibitory control (8). The Penn Emotion Recognition-40 Test assessed emotion recognition (51,52). Details of these assessments were previously published (8,50,51,53).

Structural Magnetic Resonance Imaging

T1-weighted 3T images were acquired at six sites using three different scanner brands (GE, Siemens, Philips) with similar sequences based on the Alzheimer's Disease Neuroimaging Initiative protocol (http://adni.loni.usc.edu). FreeSurfer version 6.0 was used for processing (54). In brief, scans were manually edited by trained raters to improve the segmentation of cortical and subcortical regions. Segmentation from the Desikan-Killiany atlas underwent visual inspection for motion artifacts and for proper gray/white matter segmentation, which were manually corrected. Gray matter measures for BA 17 (corresponds to V1 based on myelination in layer 4B), BA 18 (primarily corresponds to V2, also contains parts of V3 and V4) (55), and V5/MT were obtained using FreeSurfer's version 4.0.3 (legacy code in version 6.0) processing scheme, which used postmortem brains and surface-based analysis to predict visual cortical locations (56). In accordance with FreeSurfer BA labels, we used "V1" for the primary visual area (BA 17) and "V2" for the secondary visual area (BA 18). V1 was obtained using an optimal set of parameters for aligning the primary VC (57). V1 and V2 were predicted by the surrounding geometry

Table 1. Demographic and Clinical Measures

Demographics/Clinical Measures	HCs, *n* = 323	RELs, *n* = 544	Probands, *n* = 530	3-Way *p* Value
Age, Years	37.2 (12.4)	40.3 (15.6)	35.4 (12.5)	<.001
Sex, Female	177 (55.0%)	371 (68.2%)	275 (51.9%)	<.001
Race, AA/CA/OT	84/208/30	156/359/29	195/298/37	.001
Diagnosis, SZ/SZA/BPP	–	–	209/137/184	–
Antipsychotic, Yes				
First-generation antipsychotic	–	6 (1.1%)	44 (8.5%)	–
Second-generation antipsychotic	–	45 (8.4%)	389 (74.8%)	–
Daily CPZ Equivalent	–	356.3 (435.1)	437.4 (384.6)[a]	–
Age of Onset, Years	–	–	17.6 (7.8)	–
Participant Education, Years	15.0 (2.4)	14.2 (2.7)	13.5 (2.4)	<.001
WRAT-4 IQ	103.5 (13.8)	100.7 (15.3)	98.9 (15.4)	<.001
GAF	85.5 (7.5)	75.1 (13.8)	53.3 (13.9)	<.001
SFS Total	156.9 (16.0)	147.9 (21.7)	124.1 (24.5)	<.001
PANSS Total	–	–	62.9 (16.9)	
PANSS Positive Total	–	–	16.0 (5.5)	–
PANSS Negative Total	–	–	14.9 (5.3)	–
PANSS General Total	–	–	32.1 (8.9)	–
YMRS Total	–	–	6.4 (6.3)	–
MADRS Total	–	–	11.3 (9.5)	–

Values are presented as mean (SD), *n* (%), or *n*.

AA, African American; BPP, bipolar disorder with psychotic features; CA, Caucasian; CPZ, chlorpromazine; GAF, Global Assessment of Functioning; HC, healthy control; MADRS, Montgomery–Åsberg Depression Rating Scale; OT, other; PANSS, Positive and Negative Syndrome Scale; REL, first-degree relative; SFS, Birchwood Social Functioning Scale; SZ, schizophrenia; SZA, schizoaffective disorder; WRAT-4, Wide Range Achievement Test-4; YMRS, Young Mania Rating Scale.

[a]SZ, SZA, and BPP groups differed in daily CPZ equivalents (analysis of variance, $p < .001$). Daily CPZ equivalents were lower for the BPP group compared with SZ ($p = .005$) and SZA ($p = .004$) groups. There were no differences between SZ and SZA groups.

with high fidelity (56). Visual cortical segmentation maps were visually inspected for correct segmentation and rated between 0 (low quality), 1 (intermediate quality), and 2 (good quality). Low-quality scans were dropped (1 proband, 3 RELs, and 4 control subjects). Visual cortical measures greater than four standard deviations were considered outliers and dropped ($n = 6$). Winsorization of visual cortical measures was set to three standard deviations.

Plasma Inflammatory Marker Assays

Serum was isolated from a single B-SNIP site (140 probands, 60 control subjects) and assayed for IL-1β, IL-6, IL-8, IL-10, IL-12/IL-23p40, interferon gamma, TNF-α, TNF-β, CRP, Flt-1, vascular endothelial growth factor, vascular endothelial growth factor D, and complement 4a (58). Full details can be found in (58).

Familiality Estimates

Familiality estimates were determined in 330 probands and 453 RELs for bilateral V1, V2, and MT area and thickness using Sequential Oligogenic Linkage Analysis Routines, v.8.4.2, with a maximum likelihood method. A polygenic model was used while covarying for age, sex, race, scanner, and intracranial volume (for area only).

Statistical Analysis

Statistical analyses were performed in SPSS version 25.0 (IBM Corp.) and R (version 3.6.1). Demographic variables were compared across groups using χ^2 tests or analyses of variance. To compare probands and HC subjects, analyses of covariance were performed for area, thickness, and volume measures in V1, V2, and MT using total intracranial volume (for area and volume) as a covariate (model A). To assess regional specificity, group comparisons were repeated using total surface area, mean cortical thickness, or total gray matter volume as covariates (model B). Sex, race, scanner, and age were included as covariates in both models A and B. Linear mixed effects models were used to compare RELs with other groups, including family membership as a random factor and sex, race, scanner, age, and total intracranial volume (for area and volume) as fixed factors.

To compare the magnitude of visual cortical changes to other brain regions, group differences were explored for 68 brain regions using analyses of covariance (see the Supplement).

To test for differential sex effects, group-by-sex interactions were explored. For significant group-by-sex effects, comparisons were performed separately for males and females. Effect sizes were calculated using Cohen's f^2 and Cohen's d. The false discovery rate (FDR) approach was used to correct for multiple testing (q value). FDR corrections were applied separately for area, thickness, and volume. Each correction for VC measures included comparisons from six subregions (right and left V1, V2, and MT). The statistical significance was set at $q = .05$.

Associations between VC measures and clinical, cognitive, and inflammatory markers were assessed using partial

Spearman correlations because several markers were non-normally distributed. Age, race, sex, scanner, and total intracranial volume (for area and volume) were included as covariates. Peripheral inflammatory markers were additionally adjusted for storage days, hemolysis score, and assay plate. FDR corrections were applied separately for clinical (six VC subregions × seven measures) and cognitive (six VC subregions × three measures) measures. Because there are a greater number of studies reporting relationships between systemic inflammation and thickness measures compared with surface area measures, correlations were performed between inflammatory markers and thickness measures. FDR correction was performed for 13 inflammatory markers × six VC subregions. Post hoc correlations explored male and female probands separately given our significant group-by-sex interactions. Fisher's *r*-to-*z* transformation examined potential significant differences between correlations.

RESULTS

VC Morphometric Differences in Probands

Probands demonstrated lower surface area in bilateral V1 and V2 and right MT ($d = -0.14$ to -0.21) (Figure 1A; Table S1), cortical thinning in left V1 and bilateral V2 and MT ($d = -0.14$ to -0.26) (Figure 1B; Table S2), and bilateral volume loss in all three VC subregions ($d = -0.16$ to -0.23) (Figure 1C; Table S3) compared with HC subjects (model A). Subsequent analyses showed no significant differences in V1, V2, or MT measures across the three diagnostic groups (Figure S1) or B-SNIP biotypes (Supplement). There were no regionally specific area, thickness, or volume changes in VC subregions in probands versus HC subjects (model B).

Sexual Dimorphic Differences in the VC

Significant interactions between group and sex were found for bilateral V1 and V2 surface area (left V1, $q = .028$; right V1, $q = .036$; left V2, $q = .028$; right V2, $q = .028$) and volume (left V1, $q = .036$; right V1, $q = .012$; left V2, $q = .012$; right V2, $q = .012$) (model A) (Supplement). There was no significant group-by-sex interaction for V1/V2 thickness or MT measures. Female probands had smaller bilateral V1 and V2 surface area ($q < .001$, $d = -0.33$ to -0.40) (Figure 2A; Table S4) and cortical volume ($q < .001$, $d = -0.38$ to -0.46) than female HC subjects (Figure 2B; Table S5). However, there were no significant area or volume differences in V1 or V2 in male probands compared with male HC subjects.

Then, using model B, we assessed the regional specificity of sex-dependent visual cortical differences. V1 and V2 showed regional area ($q = .025$, $d = -0.22$ to -0.25) and volume ($q = .016$, $d = -0.23$ to -0.27) reductions in female probands compared with female HC subjects (Supplement). No VC structures showed regional changes in male probands compared with male HC subjects.

VC Morphometric Differences in RELs

Right MT area ($q = .03$, $d = -0.15$) and volume ($q = .012$, $d = -0.173$) were lower in RELs than HC subjects (Figure 1A; Table S6). Similarly, REL-Us demonstrated lower right MT area ($q = .03$, $d = -0.208$) and volume ($q = .018$, $d = -0.222$) compared with HC subjects. There were no thickness differences or group-by-sex interactions for RELs or REL-Us when compared with HC subjects. See the Supplement for comparisons between probands and RELs.

Familiality of VC Measures

The familiality of RELs was highest for V1 and V2 area (Table 2). Thickness familiality was lower for V1 and V2, while MT area and thickness had the lowest heritability estimates.

Associations Between VC Measures and Clinical and Cognitive Measures

In probands, V1, V2, and MT measures showed no significant associations with Positive and Negative Syndrome Scale total or subscale scores, age of illness onset, daily chlorpromazine equivalents, or Global Assessment of Functioning scores.

Significant associations were found between left MT area and BACS composite scores (direct correlations) and antisaccade error rates (inverse correlations) in all probands and in male probands (Table 3). Larger left MT volume was correlated with higher BACS total scores in all probands and in male probands. In female probands, larger V1 volumes were correlated with lower antisaccade error rates (Table 3). The associations between VC measures and cognitive markers were not significantly different among female and male probands. There were no significant associations between VC measures and cognitive measures in RELs or HC subjects.

Correlations With Peripheral Inflammation

Inverse associations were found between left V2 thickness and CRP levels in probands but not in control subjects (Fisher's $z = 1.90$, $p = .057$) (Figure 3; Table S7). When stratified by sex, female probands had an inverse correlation between CRP and left V2 thickness (Fisher's $z = 1.08$, $p = .281$) (Figure 3). No other associations were significant after FDR correction.

See the Supplement for the effects of site and antipsychotic use and effect sizes for cortical changes in other brain regions.

DISCUSSION

In this study, we demonstrated 1) significant area, thickness, and volume reductions in BA 17/V1, BA 18/V2, and V5/MT in psychosis probands; 2) lower area and volume in MT in RELs than HC subjects; 3) sex-dependent and regionally specific area and volume reductions in V1 and V2 only affecting female probands; 4) a higher degree of familiality for VC area compared with thickness; and 5) associations between lower VC measures and poor cognitive performance and greater CRP levels.

Previous studies investigating visual subregions in schizophrenia are limited, constrained by modest sample sizes, and give mixed results ranging from no V1 or V2 thickness differences (19,59) to thinning in V2 and MT (3). Thus, our findings fill the gap left by previous reports demonstrating lower area (16,21), thickness (16,17), and volume (16,60) in occipital regions in patients with psychosis. Due to the large sample size of this study, our results provide stronger evidence suggesting decreased area, thickness, and volume in all three VC subregions. The magnitude of surface area ($d = -0.14$ to -0.21),

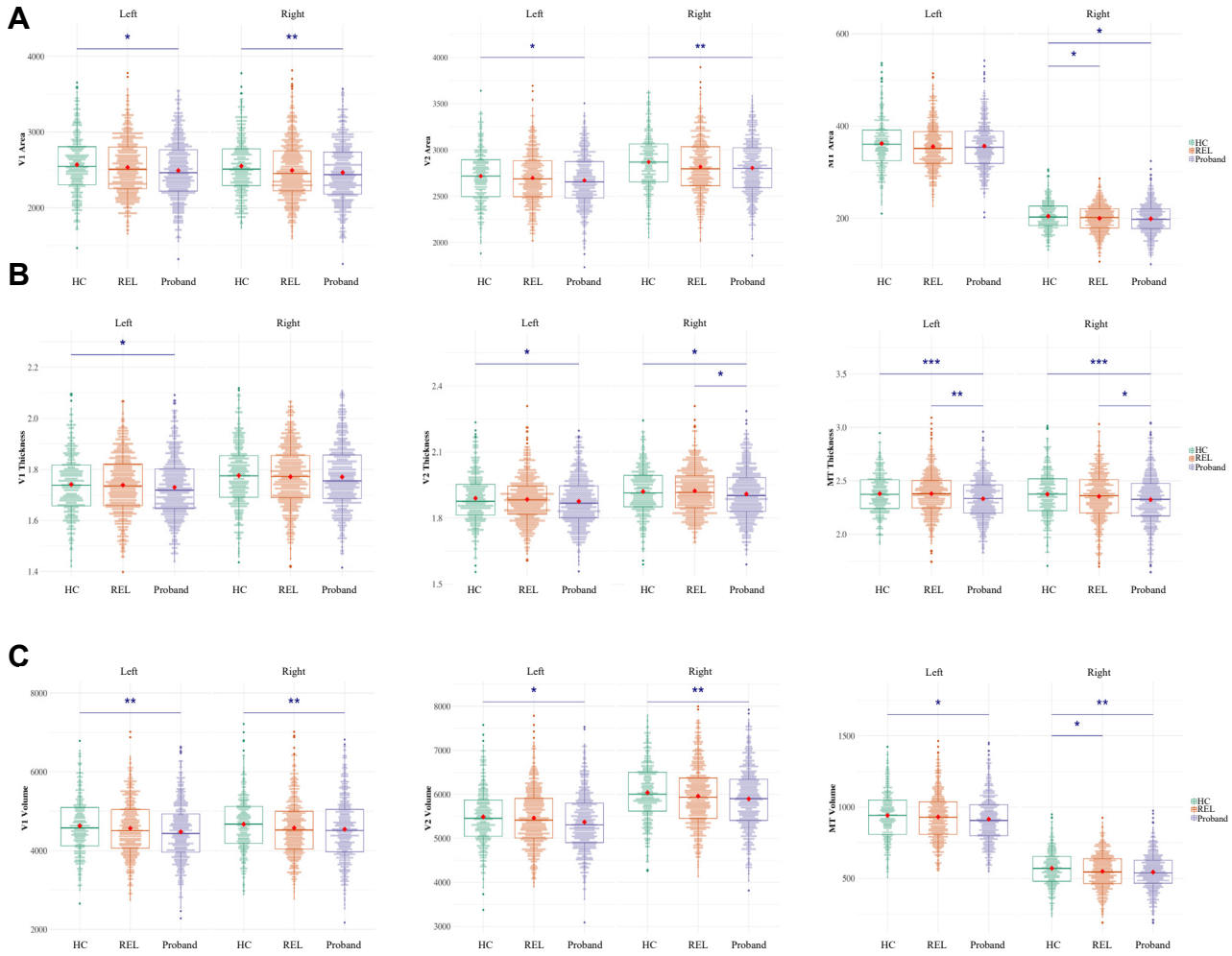

Figure 1. Comparing visual cortical area and thickness across groups. Boxplot with individual adjusted data points demonstrating group comparisons for **(A)** area (Brodmann area [BA] 17/V1, BA 18/V2, middle temporal [V5/MT]), **(B)** thickness (BA 17/V1, BA 18/V2, and V5/MT), and **(C)** volume (BA 17/V1, BA 18/V2, and V5/MT) across healthy control (HC) subjects, first-degree relatives (RELs), and psychosis probands (Proband). All imaging data were adjusted for age, sex, race, and scanner. Surface area and volume measures were additionally adjusted for total intracranial volume. Data with >4 standard deviations were considered as outliers and removed. Panel **(A)** shows significantly lower area in V1 (left: $q = .018$, $d = -0.18$; right: $q = .009$, $d = -0.21$), V2 (left: $q = .044$, $d = -0.14$; right: $q = .009$, $d = -0.2$), and MT (right: $q = .022$, $d = -0.17$) in probands compared with HC subjects. Right MT area was lower in RELs compared with HC subjects ($q = .03$, $d = -0.15$). Panel **(B)** shows significant cortical thinning in V1 (left: $q = .044$, $d = -0.14$), V2 (left: $q = .033$, $d = -0.17$; right: $q = .033$, $d = -0.16$), and MT (left: $q < .001$, $d = -0.26$; right: $q < .001$, $d = -0.26$) in probands compared with HC subjects. V2 (right: $q = .022$, $d = -0.11$) and MT thickness (left: $q = .003$, $d = -0.15$; right: $q = .022$, $d = -0.11$) were significantly lower in probands compared with RELs. Panel **(C)** shows significantly lower cortical volume in V1 (left: $q = .006$, $d = -0.20$; right: $q = .009$, $d = -0.19$), V2 (left: $q = .01$, $d = -0.18$; right: $q = .006$, $d = -0.23$), and MT (left: $q = .029$, $d = -0.16$; right: $q = .006$, $d = -0.21$) in probands compared with HC subjects. Right MT volume was lower in RELs than in HC subjects ($q = .012$, $d = -0.17$). $^{*}q < .05$; $^{**}q < .01$; $^{***}q < .001$, (◆) mean.

thickness ($d = -0.14$ to -0.26), and volume ($d = -0.16$ to -0.23) reductions in VC subregions were largely within the range of mean changes seen in other brain regions (area, $d = -0.15$ to -0.32; thickness, $d = -0.14$ to -0.41; volume, $d = -0.14$ to -0.44) (Supplement). Female probands demonstrated smaller V1 and V2 surface area ($d = -0.33$ to -0.40) and volume ($d = -0.38$ to -0.46), which also showed regional specificity. These results demonstrate significant structural impairments in VC subregions in psychosis probands, with more severe regional area and volume reductions in early visual cortices in female probands.

Surface area and cortical thickness are driven by distinct cellular processes (61–63) and show unique developmental trajectories (64). Previous research suggests that surface area trajectories in psychosis may be predominantly influenced by neurodevelopmental factors, while thickness may be more plastic and influenced by environmental and neurodegenerative factors (16,21,62). Consistent with these, we demonstrated a differential effect of area and thickness in individuals with psychosis with greater area impairments for V1 and V2, while MT, which has a delayed developmental window compared with early VCs (18), had greater thickness deficits.

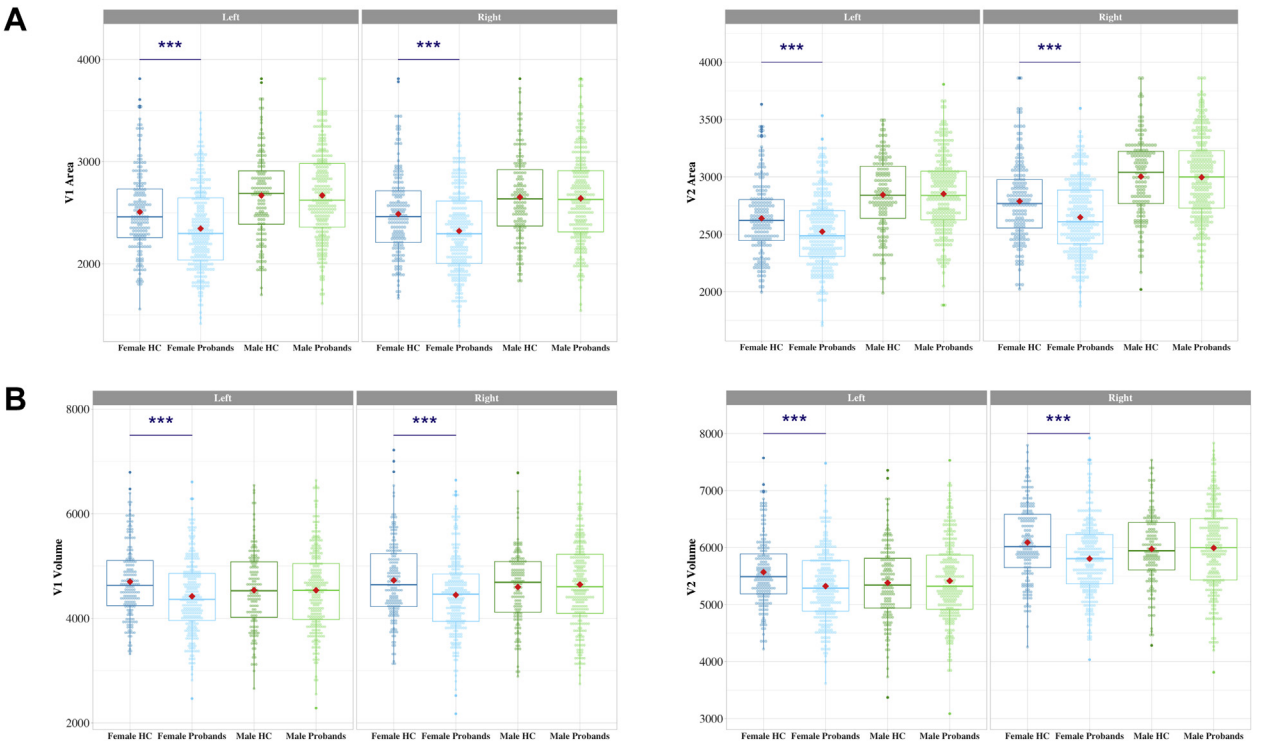

Figure 2. Sex-specific differences in Brodmann area (BA) 17/V1 and BA 18/V2 area and volume. Boxplot with individual adjusted data points demonstrating group comparisons for (**A**) BA 17/V1 and BA 18/V2 area and **(B)** BA 17/V1 and BA 18/V2 volume across healthy control (HC) subjects and psychosis probands (Proband) by sex. Surface area and volume data were adjusted for age, race, scanner, and total intracranial volume. Data with >4 standard deviations were considered as outliers and removed. Female probands had significantly reduced bilateral V1 and V2 surface area ($q < 0.001$; left V1, $d = -0.36$; right V1, $d = -0.38$; left V2, $d = -0.33$; right V2, $d = -0.40$) and cortical volume ($q < .001$; left V1, $d = -0.38$; right V1, $d = -0.40$; left V2, $d = -0.42$; right V2, $d = -0.46$) compared with female HC subjects. There were no significant area or volume differences in V1 or V2 in male probands compared with male HC subjects. ***$q < .001$, (◆) mean.

Table 2. Familiality for Visual Cortical (BA 17/V1, BA 18/V2, V5/MT) Area and Thickness

Region	h^2R	*p* Value	h^2R SE
Left V1 Area	0.713	6.6×10^{-17}	0.079
Left V1 Thickness	0.544	1.1×10^{-10}	0.083
Right V1 Area	0.709	3.6×10^{-16}	0.082
Right V1 Thickness	0.471	1.0×10^{-07}	0.088
Left V2 Area	0.632	5.7×10^{-13}	0.086
Left V2 Thickness	0.513	2.2×10^{-09}	0.087
Right V2 Area	0.629	1.8×10^{-12}	0.087
Right V2 Thickness	0.480	1.0×10^{-07}	0.089
Left MT Area	0.326	.0002	0.092
Right MT Area	0.242	.0025	0.088
Left MT Thickness	0.236	.0036	0.089
Right MT Thickness	0.311	.0003	0.091

Familiality was quantified in 330 probands and 453 of their first-degree relatives using Sequential Oligogenic Linkage Analysis Routines, version 8.4.2, with a maximum likelihood method. Significance was determined by comparing a model explaining phenotypic variation by family membership with a model assuming that family membership has no variation. Familiality estimates were calculated using a polygenic model, and visual cortical measures were covaried for age, sex, race, scanner, and intracranial volume (for surface area).

BA, Brodmann area; h^2R, residual genetic variance; MT, middle temporal.

V1 and V2 areas also had the highest familiality, which indicates a higher hereditary influence on area measures. Our results are also in line with previous studies showing that the developmental effects of sex are more pronounced in area than in thickness measures (64,65). Together, these findings indicate that VC area and thickness alterations in psychosis may result from two distinct processes that occur in different stages of life, which likely reflect the effects of distinct biological, developmental, and environmental risk factors. Therefore, these measures carry different information that may help elucidate brain biology in psychosis and inform clinical risk stratification. Sugranyes *et al.* (66) demonstrated baseline surface area deficits but no thickness deficits in familial high-risk individuals who later developed psychosis, while there was progressive cortical thinning over time, predominantly in the occipital cortex. Another study demonstrated reduced surface area but no cortical thinning in unaffected carriers of rare copy number variants associated with schizophrenia (67). Further research is needed to shed light on the mechanisms and clinical implications of these findings, such as their potential use as biomarkers of early developmental insults and risk or prognostic predictors.

The lack of differences in VC measures across DSM diagnoses is consistent with previous B-SNIP studies showing overlapping biomarker profiles across these three disorders. However, VC measures were also not different across the

Table 3. Correlations Between Cognitive Measures and VC Structural Measures

Cognitive Measure	Group	VC Measure	*r* Value	*p* Value	*q* Value
BACS Total	Probands	Left MT area	0.146	.001	.018
BACS Total	Male probands[a,b]	Left MT area	0.213	.001	.018
BACS Total	Probands	Left MT volume	0.137	.002	.036
BACS Total	Male probands[a,c]	Left MT volume	0.221	.001	.018
Antisaccade Error Rate	Probands	Left MT area	−0.136	.003	.027
Antisaccade Error Rate	Male probands[a,d]	Left MT area	−0.210	.002	.018
Antisaccade Error Rate	Female probands[a,e]	Left V1 volume	−0.201	.002	.036

Partial Spearman correlations were performed separately in probands, relatives, and HC subjects between three cognitive markers (BACS total score, antisaccade error rate, emotion recognition task score) and V1, V2, and MT area, thickness, and volume measures. Correlations were performed using age, sex, race, and total intracranial volume (only for area and volume) as covariates. Multiple comparison correction was performed separately for area, thickness, and volume measures, separately in HC subjects, relatives, and probands. *q* value = FDR-corrected *p* value. Only those cognitive and brain measures surviving multiple comparison correction are reported in the table.

BACS, Brief Assessment of Cognition in Schizophrenia; FDR, false discovery rate; HC, healthy control; MT, middle temporal; VC, visual cortex.

[a]The comparison of correlations between male and female probands.

[b]Fisher's $z = 1.32$, $q = .188$.

[c]Fisher's $z = 1.26$, $q = .207$.

[d]Fisher's $z = 1.82$, $q = .135$.

[e]Fisher's $z = 2.03$, $q = .085$.

B-SNIP biotypes, which are biologically distinct disease constructs derived from markers of high-level cognitive functions and neurophysiologic measures. In previous studies, the biotypes showed differences in gray matter volume, primarily in anterior (i.e., frontotemporal and cingulate) regions (68,69). We hypothesize that the impairments in VC measures, particularly regional changes seen in early VCs, reflect the effects of early neurodevelopmental insults, which may confer a broader predisposition to psychotic disorders. In contrast, late-developing anterior regions that control high-level cognitive functions may be more vulnerable to factors that are active in later stages of neurodevelopment, which may affect the brain in more specific ways, resulting in biological heterogeneity seen across psychotic disorders. Future research is needed to test this hypothesis and explore the temporal relationship between developmental/environmental risk factors and changes in brain biology in psychosis.

Studies show lower surface area and volume in V1 and V2 in females than in males in healthy individuals (24). Animal studies suggest a more prominent cell loss in developing female VC compared with males, which is primarily due to the effects of ovarian hormones (70). Our results demonstrating visual cortical deficits that primarily affect female probands are in line with previous studies suggesting a more pronounced sexual dimorphism in brain structure in schizophrenia (e.g., in frontomedial cortex, basal forebrain, cingulate and paracingulate gyri, amygdala) (25,27,71). In concordance with our findings, Highley *et al.* (72) observed lower occipitoparietal white matter volume in females with psychosis than in female control subjects, while males with psychosis had greater volume than male control subjects. Onitsuka *et al.* (73) demonstrated comparable V1 volumes but smaller V2 volumes in males with schizophrenia compared with male HC subjects. In contrast, despite describing smaller area in occipital regions in schizophrenia, the ENIGMA meta-analysis showed no group-by-sex interactions (21). Methodological differences in the definition of visual subregions [e.g., the broader occipital regions defined by the Desikan-Killiany atlas (74)] may be the

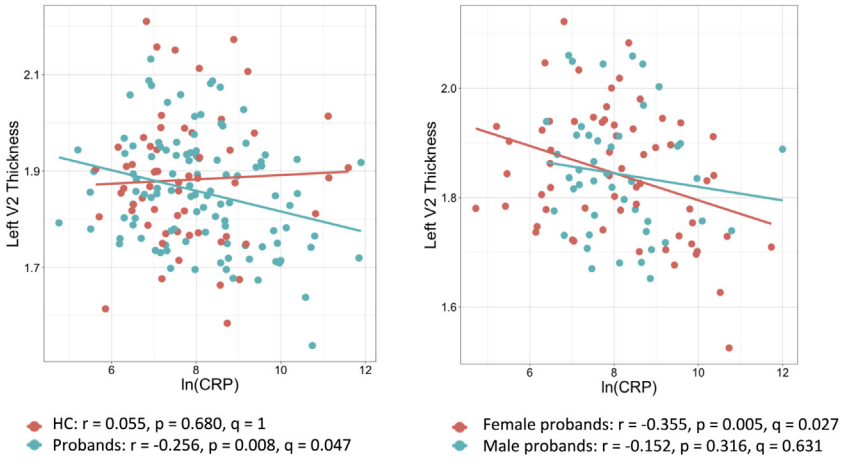

Figure 3. Peripheral inflammatory marker correlations with visual cortical thickness. Scatter plots showing pairwise Spearman correlations between the natural log of C-reactive protein (CRP) and left Brodmann area 18/V2 thickness in a subset of participants. The cytokine markers were pre-adjusted for storage days, assay set, and hemolysis score. Significant correlations ($q < .05$) are depicted here with their matched group for comparison.

reason why these studies did not capture the sex-specific effects that we demonstrated in V1 and V2. Taken together, our results support the hypothesis that neurodevelopmental effects of psychosis may potentiate the impact of physiological sex-related modifications on the VC, which results in more pronounced area and volume loss in VCs of female probands.

The significant effect of sex on VC area and volume in probands may also be related to environmental factors that distinctly affect females and males during development, such as childhood sexual abuse (75,76). Studies demonstrated a relationship between childhood trauma (i.e., sexual abuse or witnessing domestic violence) and reduced gray matter volume in the VC of young adults (77,78), with the VC being the primarily affected brain region. Future studies are needed to further explore this relationship and its effect on psychosis symptoms, such as visual hallucinations.

Our results demonstrate associations between lower MT area and volume and poorer cognitive performance, including BACS and antisaccade error task performances. MT, a region of the visual association cortex and the dorsal ("where") pathway, plays a major role in motion perception and in the generation of eye movements (79). Our findings are consistent with previous studies showing impairments in MT-related functions in schizophrenia (7) and their association with higher-level cognitive deficits (2,80). Furthermore, we demonstrate that clinical and cognitive markers are primarily associated with MT measures in probands. This is in line with the distinct developmental course of early and extrastriate visual regions. Extrastriate areas, including the MT, have a delayed development compared with early VC (18), suggesting that these regions may be more susceptible to the effects of disease processes and environmental factors that are active later in life.

In addition, we demonstrated that increased peripheral levels of CRP were associated with lower left V2 thickness in psychosis probands and female probands but not in HC subjects. Prior studies demonstrate that CRP is moderately increased in schizophrenia and is associated with positive symptoms (32). Our group recently showed higher levels of CRP in psychosis probands, which were correlated with greater Positive and Negative Syndrome Scale negative and general symptom scores and with poorer BACS and antisaccade error task performances (58). While there are no studies examining the effects of CRP on visual cortical measures in psychosis, preclinical and clinical studies demonstrate the detrimental effects of systemic inflammation on the VC, including neuronal, electrophysiological, microstructural, endothelial, and astrocytic disruptions (29,30,33–35,54,58). We also recently showed smaller cuneus (overlaps with V2) thickness with greater CRP levels in individuals with psychotic disorders (58) and structural network disruptions (greater segregation and centrality, but lower integration) of the left pericalcarine region (overlaps with V1) in first-episode psychosis subtypes with high inflammation compared with those with low inflammation (81). These studies, in conjunction with the absence of neuroinflammatory changes in the VC (39–41), suggest that systemic inflammation may negatively impact BA 18/V2 morphology (37). It is possible that environmental effects, such as trauma, may be mediating this relationship, and future studies are needed. This hypothesis is supported by a study showing that patients with bipolar disorder with inflammatory conditions (including CRP levels >5 mg/L) and reporting physical and/or sexual abuse exhibited reduced depressive symptoms with infliximab treatment compared with placebo (82).

While there are many strengths to this study, including sample size, multiple diagnostic groups, and RELs, there are also several limitations. Our psychosis sample was largely composed of chronically ill, medicated individuals. Even though there were no associations between active medication use and VC measures and no differences between probands with and without antipsychotic use, potential confounders related to chronic medication effects and medical comorbidities cannot be eliminated. In relation to peripheral inflammatory markers, we considered several major confounders (age, sex, race, assay parameters, cardiometabolic disease), but there were a number of factors (lifetime antipsychotic exposure, body mass index, trauma, and sleep-related issues) that were not measured in this study.

In conclusion, in a large multicenter sample, we demonstrated significant structural impairments in VC subregions of individuals with psychosis and their first-degree RELs, showing regional specificity in female probands and associations with cognitive impairments and peripheral inflammatory markers. These findings add to the evidence suggesting that the visual system is a significant site of pathology in psychotic disorders. Future studies exploring sex-specific effects on the VC may inform disease mechanisms by investigating effects of sex-related developmental and psychosocial factors and their interactions with other insults leading to psychotic disorders. Such research may help improve risk prediction models and support the development of novel preventive approaches for psychotic disorders.

ACKNOWLEDGMENTS AND DISCLOSURES

This work was supported by the National Institute of Mental Health (NIMH) (Grant Nos. MH-077851 [to CAT], MH-078113 [to MSK], MH-077945 [to GDP], MH-077852 [to Gunvant K. Thaker], and MH-077862 [to JAS]). HBT was supported by the NIMH (Grant No. R25MH101078). PL is supported by the National Institutes of Health (NIH) (Grant No. 1KL2TR002542), the DuPont Warren and Livingston Award from Harvard Medical School, and the Sydney R. Baer Jr Foundation. Research reported in this publication was also supported by a pilot grant to JRB from the National Center for Advancing Translational Sciences of the NIH (Grant No. ULITR000114).

We would like to thank Gunvant K. Thaker, M.D., who was closely involved with the initial stages of the B-SNIP consortium development, and was a principal investigator at the B-SNIP Maryland site (Maryland Psychiatric Research Institute, University of Maryland).

The content is solely the responsibility of the authors and does not necessarily represent the official views of NIH.

Unrelated to this work, CAT is on the Advisory Board for Karuna, KyNexis, Sunovion, Autifony, and Astellas. CAT is also a council member (unpaid) for The Brain & Behavior Research Foundation/National Alliance for Research on Schizophrenia & Depression. JAS consulted to VeraSci. MSK has been an adviser to Alkermes and Takeda. All other authors report no biomedical financial interests or potential conflicts of interest.

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Received Nov 4, 2021; revised Mar 10, 2022; accepted Mar 29, 2022.

Supplementary material cited in this article is available online at https://doi.org/10.1016/j.biopsych.2022.03.023.

REFERENCES

1. Miret S, Fatjó-Vilas M, Peralta V, Fañanás L (2016): Síntomas básicos en la esquizofrenia, su estudio clínico y relevancia en investigación [Basic symptoms in schizophrenia, their clinical study and relevance in research]. Rev Psiquiatr Salud Ment 9:111–122.
2. Türközer HB, Hasoğlu T, Chen Y, Norris LA, Brown M, Delaney-Busch N, *et al.* (2019): Integrated assessment of visual perception abnormalities in psychotic disorders and relationship with clinical characteristics. Psychol Med 49:1740–1748.
3. Schultz CC, Wagner G, Koch K, Gaser C, Roebel M, Schachtzabel C, *et al.* (2013): The visual cortex in schizophrenia: Alterations of gyrification rather than cortical thickness—A combined cortical shape analysis. Brain Struct Funct 218:51–58.
4. Silverstein SM, Berten S, Essex B, Kovács I, Susmaras T, Little DM (2009): An fMRI examination of visual integration in schizophrenia. J Integr Neurosci 8:175–202.
5. Kéri S, Kelemen O, Benedek G, Janka Z (2004): Vernier threshold in patients with schizophrenia and in their unaffected siblings. Neuropsychology 18:537–542.
6. Uhlhaas PJ, Phillips WA, Mitchell G, Silverstein SM (2006): Perceptual grouping in disorganized schizophrenia. Psychiatry Res 145:105–117.
7. Chen Y, Nakayama K, Levy DL, Matthysse S, Holzman PS (1999): Psychophysical isolation of a motion-processing deficit in schizophrenics and their relatives and its association with impaired smooth pursuit. Proc Natl Acad Sci U S A 96:4724–4729.
8. Reilly JL, Frankovich K, Hill S, Gershon ES, Keefe RSE, Keshavan MS, *et al.* (2014): Elevated antisaccade error rate as an intermediate phenotype for psychosis across diagnostic categories. Schizophr Bull 40:1011–1021.
9. Butler PD, Abeles IY, Weiskopf NG, Tambini A, Jalbrzikowski M, Legatt ME, *et al.* (2009): Sensory contributions to impaired emotion processing in schizophrenia. Schizophr Bull 35:1095–1107.
10. McBain R, Norton D, Chen Y (2010): Differential roles of low and high spatial frequency content in abnormal facial emotion perception in schizophrenia. Schizophr Res 122:151–155.
11. Green MF, Nuechterlein KH, Breitmeyer B, Mintz J (2006): Forward and backward visual masking in unaffected siblings of schizophrenic patients. Biol Psychiatry 59:446–451.
12. Uhlhaas PJ, Silverstein SM, Phillips WA, Lovell PG (2004): Evidence for impaired visual context processing in schizotypy with thought disorder. Schizophr Res 68:249–260.
13. Bressan P, Kramer P (2013): The relation between cognitive-perceptual schizotypal traits and the Ebbinghaus size-illusion is mediated by judgment time. Front Psychol 4:343.
14. Schubert EW, Henriksson KM, McNeil TF (2005): A prospective study of offspring of women with psychosis: Visual dysfunction in early childhood predicts schizophrenia-spectrum disorders in adulthood. Acta Psychiatr Scand 112:385–393.
15. Hayes JF, Picot S, Osborn DPJ, Lewis G, Dalman C, Lundin A (2019): Visual acuity in late adolescence and future psychosis risk in a cohort of 1 million men. Schizophr Bull 45:571–578.
16. Rimol LM, Nesvåg R, Hagler DJ Jr, Bergmann O, Fennema-Notestine C, Hartberg CB, *et al.* (2012): Cortical volume, surface area, and thickness in schizophrenia and bipolar disorder [published correction appears in Biol Psychiatry 2012; 71:60]. Biol Psychiatry 71:552–560.
17. Narr KL, Toga AW, Szeszko P, Thompson PM, Woods RP, Robinson D, *et al.* (2005): Cortical thinning in cingulate and occipital cortices in first episode schizophrenia. Biol Psychiatry 58:32–40.
18. Kourtzi Z, Augath M, Logothetis NK, Movshon JA, Kiorpes L (2006): Development of visually evoked cortical activity in infant macaque monkeys studied longitudinally with fMRI. Magn Reson Imaging 24:359–366.
19. Reavis EA, Lee J, Wynn JK, Engel SA, Jimenez AM, Green MF (2017): Cortical thickness of functionally defined visual areas in schizophrenia and bipolar disorder. Cereb Cortex 27:2984–2993.
20. Dorph-Petersen KA, Pierri JN, Wu Q, Sampson AR, Lewis DA (2007): Primary visual cortex volume and total neuron number are reduced in schizophrenia. J Comp Neurol 501:290–301.
21. van Erp TGM, Walton E, Hibar DP, Schmaal L, Jiang W, Glahn DC, *et al.* (2018): Cortical brain abnormalities in 4474 individuals with schizophrenia and 5098 control subjects via the Enhancing Neuro Imaging Genetics Through Meta Analysis (ENIGMA) consortium. Biol Psychiatry 84:644–654.
22. Vanston JE, Strother L (2017): Sex differences in the human visual system. J Neurosci Res 95:617–625.
23. Handa RJ, McGivern RF (2015): Steroid hormones, receptors, and perceptual and cognitive sex differences in the visual system. Curr Eye Res 40:110–127.
24. Amunts K, Armstrong E, Malikovic A, Hömke L, Mohlberg H, Schleicher A, Zilles K (2007): Gender-specific left-right asymmetries in human visual cortex. J Neurosci 27:1356–1364.
25. Abel KM, Drake R, Goldstein JM (2010): Sex differences in schizophrenia. Int Rev Psychiatry 22:417–428.
26. Goldstein JM, Cherkerzian S, Tsuang MT, Petryshen TL (2013): Sex differences in the genetic risk for schizophrenia: History of the evidence for sex-specific and sex-dependent effects. Am J Med Genet B Neuropsychiatr Genet 162B:698–710.
27. Goldstein JM, Seidman LJ, O'Brien LM, Horton NJ, Kennedy DN, Makris N, *et al.* (2002): Impact of normal sexual dimorphisms on sex differences in structural brain abnormalities in schizophrenia assessed by magnetic resonance imaging. Arch Gen Psychiatry 59:154–164.
28. Pong S, Karmacharya R, Sofman M, Bishop JR, Lizano P (2020): The role of brain microvascular endothelial cell and blood-brain barrier dysfunction in schizophrenia. Complex Psychiatry 6:30–46.
29. Gao Y, Liu L, Li Q, Wang Y (2015): Differential alterations in the morphology and electrophysiology of layer II pyramidal cells in the primary visual cortex of a mouse model prenatally exposed to LPS. Neurosci Lett 591:138–143.
30. Harrison NA, Cooper E, Dowell NG, Keramida G, Voon V, Critchley HD, Cercignani M (2015): Quantitative magnetization transfer imaging as a biomarker for effects of systemic inflammation on the brain. Biol Psychiatry 78:49–57.
31. Goldsmith DR, Rapaport MH, Miller BJ (2016): A meta-analysis of blood cytokine network alterations in psychiatric patients: Comparisons between schizophrenia, bipolar disorder and depression. Mol Psychiatry 21:1696–1709.
32. Fernandes BS, Steiner J, Bernstein HG, Dodd S, Pasco JA, Dean OM, *et al.* (2016): C-reactive protein is increased in schizophrenia but is not altered by antipsychotics: Meta-analysis and implications. Mol Psychiatry 21:554–564.
33. Lizano PL, Keshavan MS, Tandon N, Mathew IT, Mothi SS, Montrose DM, Yao JK (2016): Angiogenic and immune signatures in plasma of young relatives at familial high-risk for psychosis and first-episode patients: A preliminary study. Schizophr Res 170:115–122.
34. Cannon TD, Chung Y, He G, Sun D, Jacobson A, van Erp TGM, *et al.* (2015): Progressive reduction in cortical thickness as psychosis develops: A multisite longitudinal neuroimaging study of youth at elevated clinical risk. Biol Psychiatry 77:147–157.
35. Cai HQ, Catts VS, Webster MJ, Galletly C, Liu D, O'Donnell M, *et al.* (2020): Increased macrophages and changed brain endothelial cell gene expression in the frontal cortex of people with schizophrenia displaying inflammation. Mol Psychiatry 25:761–775.

36. Bishop JR, Zhang L, Lizano P (2022): Inflammation subtypes and translating inflammation-related genetic findings in schizophrenia and related psychoses: A perspective on pathways for treatment stratification and novel therapies. Harv Rev Psychiatry 30:59–70.
37. Di Biase MA, Zalesky A, Cetin-Karayumak S, Rathi Y, Lv J, Boerrigter D, *et al.* (2021): Large-scale evidence for an association between peripheral inflammation and white matter free water in schizophrenia and healthy individuals. Schizophr Bull 47:542–551.
38. Uranova NA, Zimina IS, Vikhreva OV, Krukov NO, Rachmanova VI, Orlovskaya DD (2010): Ultrastructural damage of capillaries in the neocortex in schizophrenia. World J Biol Psychiatry 11:567–578.
39. Selemon LD, Rajkowska G, Goldman-Rakic PS (1995): Abnormally high neuronal density in the schizophrenic cortex. A morphometric analysis of prefrontal area 9 and occipital area 17. Arch Gen Psychiatry 52:805–818; discussion 819–820.
40. Rajkowska G, Selemon LD, Goldman-Rakic PS (1998): Neuronal and glial somal size in the prefrontal cortex: A postmortem morphometric study of schizophrenia and Huntington disease. Arch Gen Psychiatry 55:215–224.
41. Kurumaji A, Wakai T, Toru M (1997): Decreases in peripheral-type benzodiazepine receptors in postmortem brains of chronic schizophrenics. J Neural Transm (Vienna) 104:1361–1370.
42. Tamminga CA, Ivleva EI, Keshavan MS, Pearlson GD, Clementz BA, Witte B, *et al.* (2013): Clinical phenotypes of psychosis in the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP). Am J Psychiatry 170:1263–1274.
43. First MB, Spitzer RL, Gibbon M, Williams JB (2002): Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition (SCID-I/P). New York: Biometrics Research, New York State Psychiatric Institute.
44. Pfohl B, Blum N, Zimmerman M (1997): Structured Interview for DSM-IV Personality: SIDP-IV. Washington, D.C.: American Psychiatric Publishing.
45. Kay SR, Fiszbein A, Opler LA (1987): The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. Schizophr Bull 13:261–276.
46. Young RC, Biggs JT, Ziegler VE, Meyer DA (1978): A rating scale for mania: Reliability, validity and sensitivity. Br J Psychiatry 133:429–435.
47. Montgomery SA, Asberg M (1979): A new depression scale designed to be sensitive to change. Br J Psychiatry 134:382–389.
48. Birchwood M, Smith J, Cochrane R, Wetton S, Copestake S (1990): The Social Functioning Scale. The development and validation of a new scale of social adjustment for use in family intervention programmes with schizophrenic patients. Br J Psychiatry 157:853–859.
49. Wilkinson GS, Robertson GJ (2006): Wide Range Achievement Test 4 (WRAT4). Lutz, FL: Psychological Assessment Resources.
50. Keefe RSE, Goldberg TE, Harvey PD, Gold JM, Poe MP, Coughenour L (2004): The Brief Assessment of Cognition in Schizophrenia: Reliability, sensitivity, and comparison with a standard neurocognitive battery. Schizophr Res 68:283–297.
51. Rubin LH, Carter CS, Bishop JR, Pournajafi-Nazarloo H, Drogos LL, Hill SK, *et al.* (2014): Reduced levels of vasopressin and reduced behavioral modulation of oxytocin in psychotic disorders. Schizophr Bull 40:1374–1384.
52. Kohler CG, Anselmo-Gallagher G, Bilker W, Karlawish J, Gur RE, Clark CM (2005): Emotion-discrimination deficits in mild Alzheimer disease. Am J Geriatr Psychiatry 13:926–933.
53. Hill SK, Buchholz A, Amsbaugh H, Reilly JL, Rubin LH, Gold JM, *et al.* (2015): Working memory impairment in probands with schizoaffective disorder and first degree relatives of schizophrenia probands extend beyond deficits predicted by generalized neuropsychological impairment. Schizophr Res 166:310–315.
54. Lizano P, Lutz O, Ling G, Lee AM, Eum S, Bishop JR, *et al.* (2019): Association of choroid plexus enlargement with cognitive, inflammatory, and structural phenotypes across the psychosis spectrum. Am J Psychiatry 176:564–572.
55. Clarke S, Miklossy J (1990): Occipital cortex in man: Organization of callosal connections, related myelo- and cytoarchitecture, and putative boundaries of functional visual areas. J Comp Neurol 298:188–214.
56. Fischl B, Rajendran N, Busa E, Augustinack J, Hinds O, Yeo BTT, *et al.* (2008): Cortical folding patterns and predicting cytoarchitecture. Cereb Cortex 18:1973–1980.
57. Hinds OP, Rajendran N, Polimeni JR, Augustinack JC, Wiggins G, Wald LL, *et al.* (2008): Accurate prediction of V1 location from cortical folds in a surface coordinate system. Neuroimage 39:1585–1599.
58. Lizano P, Lutz O, Xu Y, Rubin LH, Paskowitz L, Lee AM, *et al.* (2021): Multivariate relationships between peripheral inflammatory marker subtypes and cognitive and brain structural measures in psychosis. Mol Psychiatry 26:3430–3443.
59. Adhan I, Lizano P, Bannai D, Lutz O, Dhaliwal K, Zeng V, *et al.* (2020): Visual cortical alterations and their association with negative symptoms in antipsychotic-naïve first episode psychosis. Psychiatry Res 288:112957.
60. Mitelman SA, Shihabuddin L, Brickman AM, Hazlett EA, Buchsbaum MS (2003): MRI assessment of gray and white matter distribution in Brodmann's areas of the cortex in patients with schizophrenia with good and poor outcomes. Am J Psychiatry 160:2154–2168.
61. Rakic P (1988): Specification of cerebral cortical areas. Science 241:170–176.
62. Panizzon MS, Fennema-Notestine C, Eyler LT, Jernigan TL, Prom-Wormley E, Neale M, *et al.* (2009): Distinct genetic influences on cortical surface area and cortical thickness. Cereb Cortex 19:2728–2735.
63. Pontious A, Kowalczyk T, Englund C, Hevner RF (2008): Role of intermediate progenitor cells in cerebral cortex development. Dev Neurosci 30:24–32.
64. Wierenga LM, Langen M, Oranje B, Durston S (2014): Unique developmental trajectories of cortical thickness and surface area. Neuroimage 87:120–126.
65. Raznahan A, Shaw P, Lalonde F, Stockman M, Wallace GL, Greenstein D, *et al.* (2011): How does your cortex grow? J Neurosci 31:7174–7177.
66. Sugranyes G, de la Serna E, Ilzarbe D, Pariente JC, Borras R, Romero S, *et al.* (2021): Brain structural trajectories in youth at familial risk for schizophrenia or bipolar disorder according to development of psychosis spectrum symptoms. J Child Psychol Psychiatry 62:780–789.
67. Caseras X, Kirov G, Kendall KM, Rees E, Legge SE, Bracher-Smith M, *et al.* (2021): Effects of genomic copy number variants penetrant for schizophrenia on cortical thickness and surface area in healthy individuals: Analysis of the UK Biobank. Br J Psychiatry 218:104–111.
68. Ivleva EI, Clementz BA, Dutcher AM, Arnold SJM, Jeon-Slaughter H, Aslan S, *et al.* (2017): Brain structure biomarkers in the psychosis biotypes: Findings from the bipolar-schizophrenia network for intermediate phenotypes. Biol Psychiatry 82:26–39.
69. Clementz BA, Sweeney JA, Hamm JP, Ivleva EI, Ethridge LE, Pearlson GD, *et al.* (2016): Identification of distinct psychosis biotypes using brain-based biomarkers [published correction appears in Am J Psychiatry 2016; 173:198]. Am J Psychiatry 173:373–384.
70. Nuñez JL, Sodhi J, Juraska JM (2002): Ovarian hormones after postnatal day 20 reduce neuron number in the rat primary visual cortex. J Neurobiol 52:312–321.
71. Gur RE, Kohler C, Turetsky BI, Siegel SJ, Kanes SJ, Bilker WB, *et al.* (2004): A sexually dimorphic ratio of orbitofrontal to amygdala volume is altered in schizophrenia. Biol Psychiatry 55:512–517.
72. Highley JR, DeLisi LE, Roberts N, Webb JA, Relja M, Razi K, Crow TJ (2003): Sex-dependent effects of schizophrenia: An MRI study of gyral folding, and cortical and white matter volume. Psychiatry Res 124:11–23.
73. Onitsuka T, McCarley RW, Kuroki N, Dickey CC, Kubicki M, Demeo SS, *et al.* (2007): Occipital lobe gray matter volume in male patients with chronic schizophrenia: A quantitative MRI study. Schizophr Res 92:197–206.
74. Desikan RS, Ségonne F, Fischl B, Quinn BT, Dickerson BC, Blacker D, *et al.* (2006): An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. Neuroimage 31:968–980.

75. Fergusson DM, Lynskey MT, Horwood LJ (1996): Childhood sexual abuse and psychiatric disorder in young adulthood: I. Prevalence of sexual abuse and factors associated with sexual abuse. J Am Acad Child Adolesc Psychiatry 35:1355–1364.
76. Bebbington P, Jonas S, Kuipers E, King M, Cooper C, Brugha T, *et al.* (2011): Childhood sexual abuse and psychosis: Data from a cross-sectional national psychiatric survey in England. Br J Psychiatry 199:29–37.
77. Tomoda A, Navalta CP, Polcari A, Sadato N, Teicher MH (2009): Childhood sexual abuse is associated with reduced gray matter volume in visual cortex of young women. Biol Psychiatry 66:642–648.
78. Tomoda A, Polcari A, Anderson CM, Teicher MH (2012): Reduced visual cortex gray matter volume and thickness in young adults who witnessed domestic violence during childhood. PLoS One 7:e52528.
79. Born RT, Bradley DC (2005): Structure and function of visual area MT. Annu Rev Neurosci 28:157–189.
80. Park S, Holzman PS (1993): Association of working memory deficit and eye tracking dysfunction in schizophrenia. Schizophr Res 11: 55–61.
81. Hoang D, Xu Y, Lutz O, Bannai D, Zeng V, Bishop JR, *et al.* (2022): Inflammatory subtypes in antipsychotic-naïve first-episode schizophrenia are associated with altered brain morphology and topological organization. Brain Behav Immun 100:297–308.
82. McIntyre RS, Subramaniapillai M, Lee Y, Pan Z, Carmona NE, Shekotikhina M, *et al.* (2019): Efficacy of adjunctive infliximab vs placebo in the treatment of adults with bipolar I/II depression: A randomized clinical trial. JAMA Psychiatry 76:783–790.