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Choroid Plexus Enlargement is Associated with Cognitive, Inflammatory and Structural Phenotypes Across the Psychosis Spectrum

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Abstract

Objective: The choroid plexus (CP) is an important physiological barrier and produces cerebrospinal fluid, neurotrophic, angiogenic, and inflammatory factors involved in brain development. CP abnormalities have also been implicated in both schizophrenia and bipolar disorder. A CP transcriptomic analysis in schizophrenia identified an upregulation of immune/inflammatory genes that correlated with peripheral inflammatory markers. Our goal was to

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Supplementary Figure 1: Choroid plexus volume correlations with BACS subscale scores in probands, first-degree relatives and healthy controls (NC). Partial correlations were adjusted for age, sex, race, site. Imaging data was additionally adjusted for total intracranial volume. FDR corrected q-values.

examine 1) CP volume across psychotic probands, their first degree and Axis-II A relatives, 2) CP familiarity, and 3) CP covariance with clinical, cognitive, brain, and peripheral marker measures.

Method: CP volume was quantified using FreeSurfer 6 in psychosis probands, their first degree and Axis-IIA relatives, and healthy subjects organized by DSM-IV-TR diagnosis (n=1,451). Analyte, structural connectivity and genotype data were collected from a subset of subjects.

Results: CP volume was significantly larger in probands compared to controls, first-degree relatives had significant intermediate CP volume between probands and controls, and total CP volume was significantly heritable. Larger CP volume was associated with worse cognition, smaller total gray matter and amygdala volume, larger lateral ventricle volume, and lower structural connectivity in probands. We also found associations between larger CP volume and higher levels of IL6 in probands.

Conclusion: Our findings suggest the involvement of the CP across the psychosis spectrum with a potential pathophysiological mechanism involving the neuro-immune axis, which functions in maintaining brain homeostasis and interacting with the peripheral immune and inflammatory system. The CP may be an important target for future research.

Introduction

The choroid plexus (CP) has been largely ignored in clinical neuroscience, but recent evidence suggests that it plays several important roles in brain homeostasis. The CP is located in the lateral, third and fourth ventricles and produces cerebrospinal fluid (CSF). The CP consists of an epithelial cell monolayer which forms a physical barrier called the blood–CSF barrier, and a stromal compartment containing permeable fenestrated blood vessels, as well as immune, pluripotent, hematopoietic, neuronal progenitor and telocyte cells (1,2). The choroid plexus epithelium limits the paracellular passage via tight junctions and allows intercellular communication through gap junctions (3). Transport across the blood–CSF barrier is tightly controlled involving both active and passive transport, which plays an important role in cell division, migration, differentiation and synaptogenesis during early brain development (4,5). The blood–CSF barrier can function as an enzymatic barrier with the ability to conjugate drugs and other proteins assisting in elimination and providing protection against oxidative stress (6). Also, the blood–CSF barrier is an immunological barrier with resident immune cells that can modulate leukocyte migration, produce pro-inflammatory cytokines, expresses major histocompatibility complex molecules and molecules for leukocyte adhesion (6). Lastly, the lateral ventricle CP secretes chemokines, lymphokines, growth factors, carriers, and remodelers that promote the proliferation of neural stem cells (1,7–9), and the CP epithelium transcriptome specifically functions in molecular transport, neurological disease processes, immunological functions, ciliary movement, hematopoiesis and angiogenesis (10). While our understanding of the role of the CP in brain homeostasis is growing, much less is known about its role in psychotic disorders, despite the intersection between CP function and the neurodevelopmental, neurodegenerative, and neuro-immune hypotheses in psychosis pathophysiology.

CP abnormalities have been discussed as a possible pathological feature in schizophrenia and bipolar disorder beginning with Morawoka and Kitabayashi in 1921, where

morphological changes in choroid plexus epithelium (smaller and longer cells), vascular endothelium degeneration, large cystic formations, and cellular fat depositions in CP epithelium cells were identified in schizophrenia, while evidence of CP epithelium hypersecretion and degeneration of vascular epithelium and connective tissue were found in bipolar mania as compared to healthy controls (11,12). However, despite these findings the role of the CP in psychosis has been largely ignored. More recently, case reports have identified an association between worse cognition (memory difficulties and inattention), mood (depression, anhedonia, lethargy, isolation, and suicidal ideation), and psychosis (persecutory delusions, ideas of reference, auditory hallucinations, hostility, blunted affect, poverty of speech, emotional/social withdrawal and motor retardation) with fourth ventricle CP papilloma or third ventricle tumor, which resulted in full symptom remission after tumor resection (13–15). Moreover, cross-sectional studies using CT brain imaging have identified an association between the presence of CP calcification and schizophrenia neurobiology (16–19), but no brain MRI studies examining CP volume in schizophrenia exist to date. Previous, imaging studies have identified an association between increased CP calcification size and greater hallucination intensity, worse formal thought disorder, regional brain volume reductions (frontal, temporal, parietal, hippocampal, and cerebellar), and larger ventricular brain ratio at the frontal horns, but less is known regarding negative symptoms or cognitive dysfunction (16,18,19). In schizophrenia, a recent transcriptomic analysis of the CP found that a co-expression module of immune and inflammation genes was upregulated and this module was significantly associated with disease status and positively correlated with C-reactive protein (CRP), cortisol, and pro-inflammatory cytokines in the serum and frontal cortex of the same individuals (20). Therefore, these findings suggest that the increased size of the CP might be involved in psychosis phenomenology (positive, negative, and cognitive symptoms), neurobiology (regional volumetric reductions), and neuro-immune axis connection, but more research is needed to further our understanding of the role of the CP across the psychosis spectrum.

Taken together, we sought to investigate 1) CP volume across psychotic disorder probands, their first-degree and Axis IIA relatives, and healthy subjects, 2) CP familiarity between probands and their first-degree relatives, and 3) CP covariance with clinical, brain, and peripheral marker measures using data from the cross-sectional Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP) consortium. We hypothesize that CP volume is increased in psychosis and is heritable, and that increased CP volume is associated with worse psychosis symptoms and cognition, correlated with regional brain atrophy, and is related to increased levels of peripheral inflammatory markers.

Methods

Participants

A subset of participants for whom FreeSurfer analyses could be completed were included from the B-SNIP multisite study that included Harvard University, Wayne State University, Maryland Psychiatric Research Center, University of Chicago, University of Texas Southwestern Medical Center at Dallas and Institute of Living/Yale University. The study protocol was approved by the institutional review board at each local site. Probands with

diagnoses of schizophrenia (SZP), schizoaffective disorder (SADP), or psychotic bipolar I disorder (BPP), at least one of each proband's first-degree relatives, and healthy control (NC) subjects (21) were recruited and provided written consent (see supplementary methods for inclusion criteria).

The Structured Clinical Interview for DSM-IV (SCID-IV) was administered to all subjects and a consensus diagnosis was made using clinical interviews, medical records and psychiatric histories. Relatives were assessed with the Structured Interview for DSM-IV Personality Disorders (SIDP-IV) to evaluate personality traits specifically relevant to the psychosis spectrum, represented by the cluster A personality disorders (21). Average daily chlorpromazine (CPZ) equivalents were generated and antipsychotics were categorized into first generation and second generation antipsychotic classes (Table 1). Probands were administered the Positive and Negative Symptom Scale (PANSS) and Montgomery-Asberg Depression Rating Scale (MADRS). Cognition was evaluated using the Brief Assessment of Cognition (BACS) battery (22) and all scores were adjusted for age and sex and z-transformed to a range of ± 4.0 . The Birchwood Psychosocial Function Scale (SFS) was used to capture social functioning in all groups. For group sample size by clinical measure see ST1.

Structural MRI

Subjects were scanned at all six sites and T1 MPRAGE images were processed using FreeSurfer 6.0 (see supplementary methods for imaging protocol). Forty-seven participants were removed for scanner inhomogeneity and motion that interfered with segmentation. Participants with greater than four standard deviations ($n=6$) and between the third and fourth standard deviation ($n=19$) were removed and winsorised to the third standard deviation, respectively. To examine the relationship between CP volume and the dysconnectivity hypothesis in psychosis, we ran an exploratory analysis of diffusion weighted images to extract the average tissue fractional anisotropy (FA_t) in a subset of subjects (Probands, $n=131$; and Relatives, $n=140$, see supplementary methods). Healthy control subjects were not included in this analysis due to the small sample size ($n=42$).

Since few studies have published on CP volume using FreeSurfer, two raters (PL and OL) established reliability using manual ratings for the scans. The CP for 24 raw scans (4 per site) were randomly and blindly manually rated for small, medium and large volumes. The raters had a high intra-class correlation coefficient for their ratings ($ICC=0.79$) and moderate Spearman correlations with FreeSurfer volume ($r=0.44$, $p < 0.01$).

Plasma analyte assays

Blood samples from the Chicago site were obtained from 107 psychosis probands (BPP, $n=48$; SADP, $n=23$; SZP, $n=36$) and 58 healthy controls at baseline, batched, spun at 4°C , divided into $300\mu\text{l}$ aliquots, and stored at -80°C . The plasma concentrations of inflammatory/ neurotrophic (IL- 1β , IL2, IL4, IL6, IL8, IL10, IL12, IL12p70, IFN γ , TNF α , CRP, sFlt-1, VEGF, TGF β) markers were determined using MESO SCALE DISCOVERY'S (MSD) MULTI-ARRAY® Technology. These analytes were selected based on their implication in schizophrenia and bipolar disorder (23–29). See supplementary methods for

analyte quality control. See ST1 for a breakdown of the number of subjects assayed by analyte and by group.

Statistical Analysis

Descriptive statistics were computed for demographic variables across groups and differences were examined using χ^2 test or analysis of variance (ANOVA). Pairwise contrasts using analysis of covariance (ANCOVA) to assess CP volume were run on probands, first-degree relatives (Relatives), Axis II Cluster A family members (Axis IIAR) and NC. An exploratory analysis of diagnostic (SZP, SADP, and BPP) groups compared to NC was performed to determine if a particular group was driving the effect.

Effect sizes were calculated using Cohen's d. Partial correlations for clinical, cognitive, analyte and neuroimaging measures were analyzed using Spearman (non-normal distribution for several variables). Calculated p-values were false discovery rate (FDR) corrected for multiple comparisons (q-value) and this was performed for each hypothesis tested, as well as for exploratory analyses. All data were adjusted for age, sex, race and site. Imaging data were additionally adjusted for total intracranial volume (ICV). To examine whether CP volume is determined by total lateral ventricle volume and/or total gray matter volume we performed CP group comparisons using total lateral ventricle volume and total lateral ventricle volume plus total gray matter volume instead of ICV as a covariate to regress out the effects of cortical atrophy and ventricular enlargement. Analyte data were additionally adjusted for storage days. All statistical analyses were performed using R (version 3.4.3).

Familiality for total CP volume was quantified in 340 probands and 464 of their first-degree relatives using Sequential Oligogenic Linkage Analysis Routines (SOLAR) version 8.1.4 with a maximum likelihood method. Significance was determined by comparing a model explaining phenotypic variation by family membership to a model assuming family membership has no variation. Familiality estimates were calculated using a polygenic model and CP volume was covaried for age, sex, race, site, and ICV.

Results

Demographics

Our final sample included 554 probands (diagnostic groups: SZP, n=223; SADP, n=141; BPP, n=190), 522 first-degree relatives, 42 Axis IIAR, and 334 NC (Table 1, ST5). The probands, family members and NC were matched for ICV but significantly differed for age, sex, and race (Table 1). The diagnostic groups showed no differences for age, but were significantly ($p<0.001$) different for sex, race, duration of illness, age of onset and ICV (ST2). PANSS total score were in the moderate range (>58 and 75) for the proband group (Table 1). PANSS total score were in the mild (58) and moderate range for the diagnostic groups, and they were significantly different between the three diagnostic groups (ST2) (30). Daily CPZ equivalents were not significantly different between the three diagnostic groups (ST2). Many of the probands were on second generation antipsychotics (n=406), fewer on first generation (n=48), none were taking both first and second-generation antipsychotics, and the remaining weren't taking any antipsychotic medications (n=90) (Table 1).

Choroid plexus volumetric differences

Probands had significantly larger bilateral CP volume compared to NC ($q < 0.001$, Cohen's $d = 0.335$ and 0.301 for left and right, respectively, Figure 1A, ST3 and ST4) and these results remained significant after covarying for lateral ventricle volume ($q < 0.05$, Cohen's $d = 0.193$ and 0.162 for left and right respectively) or lateral ventricle volume plus total gray matter volume ($q < 0.05$, Cohen's $d = 0.188$ and 0.181 for left and right respectively). Probands had significantly greater bilateral CP volume compared to first-degree relatives (Figure 1A, left CP $q < 0.001$, Cohen's $d = 0.226$; right CP $q < 0.001$, Cohen's $d = 0.205$) but these results were no longer significant after covarying for lateral ventricle volume with or without total gray matter volume (ST4). There were no significant CP volume differences between first-degree relatives and NC (Figure 1A)., Probands showed a non-significant increase in the left CP volume (Cohen's $d = 0.254$) compared to Axis IAR. while Axis IAR demonstrated a non-significant bilateral enlargement (Cohen's $d = 0.09-0.25$) compared to NC (ST5).

Since greater CP volume was observed bilaterally in probands, subsequent analyses assessed total CP volume by summing the corresponding left and right CP volumes. All three diagnostic groups (SZP, SADP and BPP) displayed greater total CP volume compared to NC ($q < 0.001$, Cohen's $d = 0.315$ to 0.386 for diagnostic groups, Figure 1B, ST4). When including lateral ventricle volume as a covariate instead of ICV, then SZP and BPP (Cohen's $d = 0.192$, 0.252 , respectively, ST4) remained significantly larger than NC ($q < 0.05$) while SADP did not. A similar pattern was noted when including lateral ventricle and total gray matter volume as covariates instead of ICV (SZ, Cohen's $d = 0.198$; BPP, Cohen's $d = 0.259$, see ST4) and this was significantly ($q < 0.05$) different from controls.

Total CP volume was found to be moderately heritable (Log likelihood = -5039.68 , h^2_R is 0.297 , standard error = 0.087 , $p < 0.001$, kurtosis 0.570).

CP volume correlations with clinical variables

PANSS positive total score and negative total score, age of onset and daily chlorpromazine equivalents displayed no significant relationships in probands (ST6). To address the dopamine and serotonin link to CP (31,32), we explored the relationship of antipsychotics that are predominantly dopamine antagonism (first-generation antipsychotics) versus serotonin-dopamine antagonists (second-generation antipsychotics) on CP volume. There was no significant relationship ($p = 0.25$, $F = 1.38$, $df = 2$) between first-generation (CP volume mean = 1089.4 and $SD = 304.2$), second-generation (CP volume mean = 1141.9 and $SD = 327.6$), and no antipsychotic use (CP volume mean = 1097.4 and $SD = 329.5$) in our sample. SFS total was not significantly related to CP volume in the probands, first-degree relatives or NC (Figure 2A, ST7), as well as Axis IAR (ST5).

CP volume correlations with Cognition

Larger CP volume had a significant ($r = -0.11$, $q < 0.05$), relationship with worse BACS composite scores in probands, but not in family members or NC (Figure 2A, ST7). For subcategories within the BACS, probands showed significant associations between greater CP volume and lower performance in verbal fluency ($r = -0.132$, $q < 0.05$) and symbol coding

($r=-0.109$, $q<0.05$), but not for other subdomains or in NC, relatives (SF1, ST7) and Axis IAR (ST5).

CP volume correlations with brain structure

Larger CP volume significantly ($q<0.001$) correlated with larger lateral ventricle volume in all three groups (Figure 2B, ST8). Lower total gray matter volume displayed a significant ($q<0.01$) relationship with larger CP volume in probands and first-degree relatives. Smaller amygdala volume had a significant ($q<0.01$), relationship with bigger CP volume in probands and relatives. First degree relatives demonstrated a relationship between larger CP volume and smaller hippocampal volume ($q<0.05$). NC showed a significant ($q<0.05$) correlation between higher CP volume and higher caudate volume (ST8). Axis IAR had significant ($q<0.05$) positive relationships between larger CP volume and bigger lateral ventricle or larger caudate volume (ST5). No significant relationships were observed between CP volume and cerebellum cortex volume.

In examining the relationship between CP volume and brain structural connectivity, it was observed that in a subset of our neuroimaging sample that increased CP volume was significantly negatively associated with global FAT ($p=0.012$, Figure 3) in probands and this same relationship was not seen in relatives.

CP volume correlations with analytes

Elevations in IL6 was associated ($r=0.23$, $p=0.02$, uncorrected) with larger CP volume in probands, but not controls (Figure 4A and 4B, ST9). To test the effect of clinical condition we examined diagnostic group differences and found that greater levels of IL6 ($r=0.31$, $p=0.04$) and IL10 ($r=0.36$, $p=0.01$) were associated with larger CP volume in the BPP group, while greater IL4 levels were associated with smaller CP volume ($r=-0.30$, $p=0.04$) in controls (ST9). No other significant correlations were observed between CP volume and remaining analytes in the proband, diagnostic or NC groups. To address whether IL6 levels were associated with symptom severity, we performed a Spearman correlation between IL6 levels and PANSS total score or MADRS total score and no relationship was observed ($r=0.059$, $p=0.542$ and $r=0.021$, $p=0.833$, respectively).

Discussion

In summary, we found that 1) bilateral CP volume was significantly larger in probands compared to controls and was independent of diagnostic category, 2) first-degree relatives had significant intermediate bilateral CP enlargement between probands and controls and 3) total CP volume was significantly heritable. We also demonstrated associations between larger CP volume and worse composite cognitive score, which was primarily driven by poorer performance in verbal fluency and digit symbol coding in probands. We did not observe any associations between CP size and positive or negative symptoms of psychosis or social functioning. Similarly, we established that greater CP volume was related to smaller total gray matter and amygdala volume, larger lateral ventricle volume, and lower structural connectivity in probands. Additionally, we uncovered an important association between larger CP volume and higher levels of IL6 in probands. Finally, we identified a candidate

SNP (rs112819629) on chromosome 3p14.2 that was associated with total CP volume. Our results support our hypothesis that CP enlargement exists across psychotic disorders and that it is related to clinical and neuroimaging phenotypes observed in psychosis, which include cognitive impairment, brain atrophy, brain structural dysconnectivity, and increased inflammation.

Our finding of greater CP volume in psychosis suggests that the CP may be a common trait shared across the psychosis spectrum. Since this is the first brain structural MRI study examining CP volume in psychotic disorders, estimates of CP structural alterations do not exist. However, postmortem studies in schizophrenia and bipolar disorder have described morphological changes in the CP, such as smaller and longer epithelial cells, large cystic formations, epithelial cellular fat depositions, and epithelial hypersecretion, which would suggest that CP enlargement is a pathological feature of psychosis (11). Additionally, evidence supporting this hypothesis has come from observations of CP enlargement due to tumor formation or calcifications, which have shown that increased CP size is associated with worse symptoms of cognition, mood, and psychosis, as well as a pattern of regional brain atrophy similar to schizophrenia (13–19).

While we observed an increase in CP volume in psychosis, this information was not sufficient to enhance our understanding of the pathophysiological role of CP enlargement in psychosis, which could be hypothesized to include a neurodevelopmental, neurodegenerative, neuro-immune or the effect of antipsychotic medications. In this study, we ruled out the effect of comorbidity of medication, such as antipsychotic dosage or antipsychotic class on CP volume and our finding was consistent with preclinical studies showing that infusion with dopamine or serotonin increases CP blood flow, and that dopamine receptor blockade reduces flow, but that it doesn't necessarily change the CP volume (31,32). From a neurodevelopmental and neurodegenerative standpoint, we were not able to determine whether our CP volume finding was due to hypersecretion, decreased absorption, or other morphological changes due to limitations in structural brain imaging, which could explain the well-known finding of ventricular enlargement and/or cortical atrophy. However, we were able to show that CP volume was both independently and significantly increased in probands compared to controls after controlling for lateral ventricle volume or lateral ventricle volume plus total gray matter volume. Lateral ventricle enlargement and cortical atrophy is a well-established finding in schizophrenia and bipolar disorder, and our findings suggest that the CP is a more specific determinant of psychosis proneness and that it may contribute to lateral ventricle enlargement through a currently unknown mechanism. It remains to be determined whether CP enlargement is a cause or consequence of psychosis and this question could not be fully ascertained with our cross-sectional study. Thus, our findings suggest that CP alterations may be involved in psychosis and it would be important for future studies to identify whether the CP plays a pathogenic role, is governed by ventricular enlargement via cortical atrophy, is progressively increasing over the course of the illness, and whether it is specific to psychosis by examining non-psychotic bipolar I disorder or major depressive disorder groups.

Another important pathophysiologic mechanism involves the neuro-immune connection and its role in brain homeostasis. Thus, we examined the relationship between serum markers

and CP volume, since the CP links peripheral signaling (inflammatory, angiogenic, and neurotrophic) to CNS molecular processes, which may contribute to the development and progression of psychotic disorders (20,26,33,34). We found that increased IL6 levels were significantly associated with larger CP volume. This finding is of interest since the CP expresses the receptor for IL6 (35) and in the blood IL6 has pleiotropic activity which induces the synthesis of acute phase proteins (e.g CRP), activates the acquired immune response by stimulating antibody production and effector T-cell development, and can promote the differentiation/proliferation of nonimmune cells (36). It is important to note that IL6 elevations are strongly implicated in schizophrenia and bipolar pathophysiology (25) and that cortical gray matter reductions (assessed in post mortem samples) in schizophrenia is exaggerated in patients with high expression of inflammatory cytokines (37). In further support of this hypothesis, a schizophrenia postmortem CP transcriptome study identified an immune/inflammation module that significantly positively correlated with serum CRP levels, which is downstream from IL6 (20). Lastly, a preliminary study by Zhou et al 2015 showed that CP volume was increased in patients with chronic regional pain syndrome compared to controls and they postulated that this finding was due to inflammatory processes (38). While this novel finding may suggest that CP enlargement is due to inflammatory pathways in any disorder rather than being specific to psychosis, we believe that their small sample size and lateralization of their findings, suggest that more work is needed before concluding that CP enlargement is specific to inflammatory activation in any disorder. Thus, IL6 and CRP may play a role in stress-immune related pathways leading to immune activation and vascular dysfunction that can have detrimental CNS effects (25). The positive relationship between CP volume and IL6 provides further support that the CP links the peripheral and CNS environments. However, additional work is needed to better understand the significance of peripheral immune and inflammatory markers on CP structural alterations.

The association between the CP neuro-immune axis and our brain structural and cognitive findings are further supported by our covariance analysis. Studies have shown that increased levels of inflammation are associated with reductions in cortical gray matter volume (37). Additionally, neuroinflammation has been associated with white matter pathology and it may contribute to structural and functional dysconnectivity in psychosis (39). Lastly, animal studies have demonstrated that CD4+ T cells in the CP are responsible for cognitive functions such as spatial learning and memory, and that these CD4+ T cells accumulate during mental stress (40). Taken together, the association between higher levels of IL6 and increased CP volume, could explain the association between greater CP volume and total gray matter thinning, amygdala atrophy, ventricular enlargement, and lower structural connectivity, and these changes may culminate in worse cognition. This axis might be triggered by mental stress, which would activate a neuro-immune cascade with significant downstream effects on cognition and brain structure.

A discussion of the familiarity findings can be found in the supplemental discussion material.

To our knowledge, this is the first report of alterations in CP volumes across the psychosis spectrum. A major strength of this study is an automated parcellation approach with high

intra-class correlations between raters (PL and OL) and moderate correlations with FreeSurfer CP volume. Another strength is the large, clinically well-characterized sample of patients across the psychosis spectrum. However, the subsample was not large enough to detect robust relationships with peripheral makers and genome-wide associations. Nevertheless, our results provide the first study examining the role of CP structure in psychotic disorders which can inform future studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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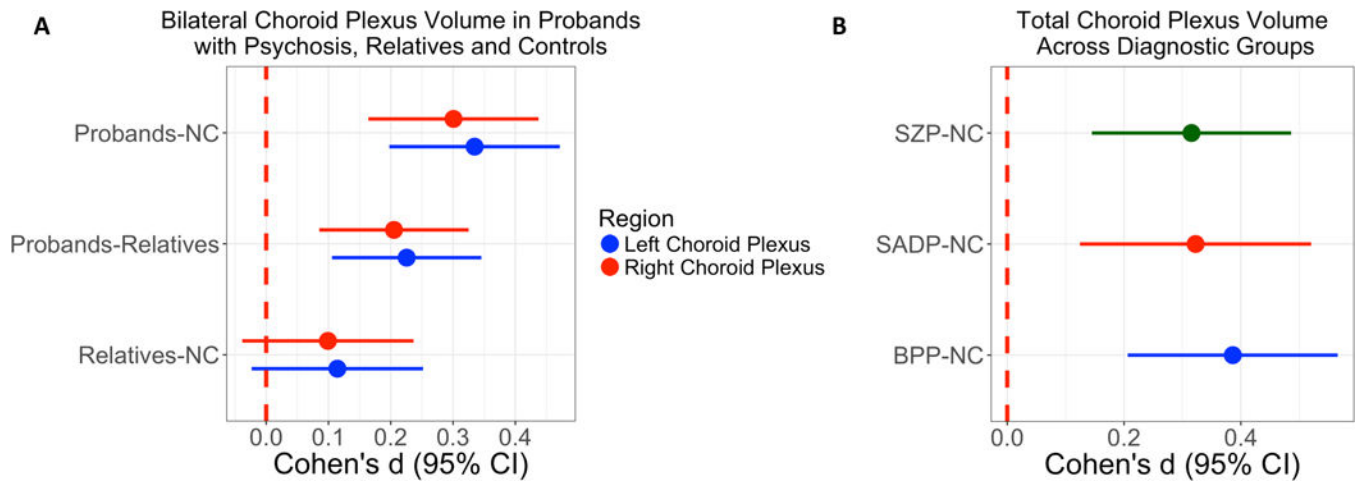


Figure 1.

Effect sizes for choroid plexus volume comparisons. 1A) Pairwise contrasts between probands, first-degree relatives, and healthy controls (NC) for bilateral choroid plexus volume. 1B) Comparisons of total choroid plexus volume for schizophrenia (SZP), schizoaffective (SADP), and psychotic bipolar I disorder (BPP) compared to NC. Dot indicates Cohen's d and lines indicate confidence intervals (CI). Cohen's d estimates were adjusted for age, sex, race, site, and intracranial volume.

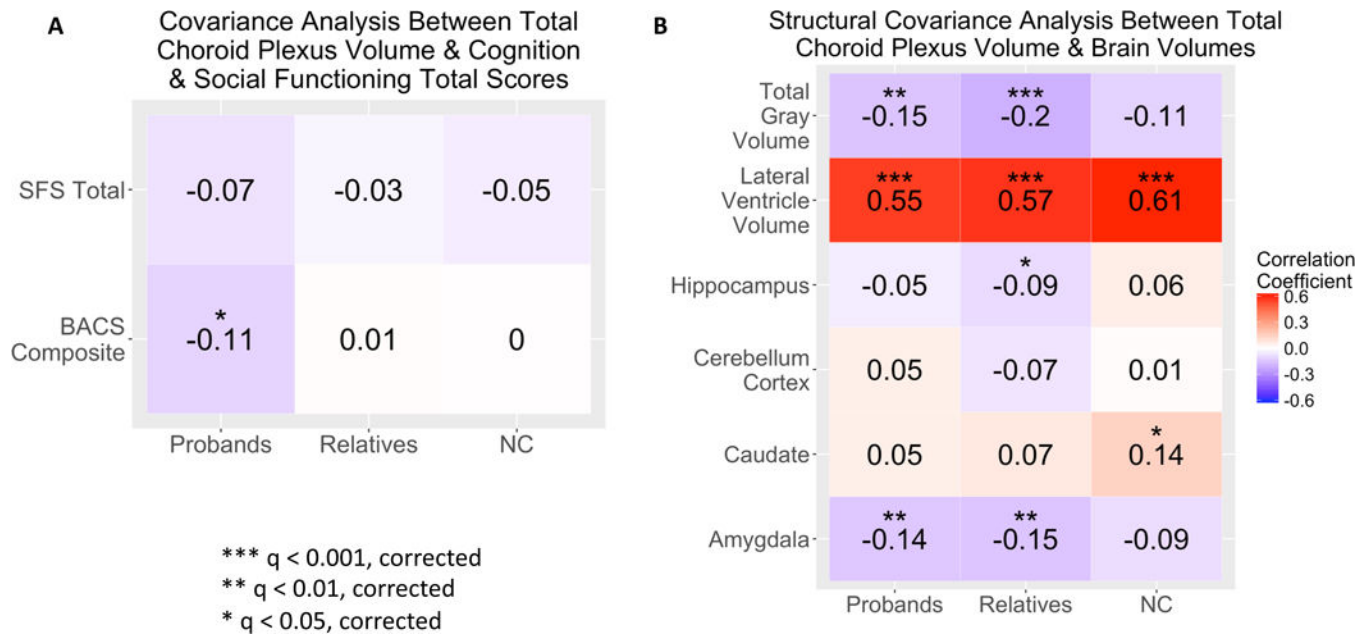


Figure 2. Choroid plexus volume correlations with clinical and brain structural measures in probands, first-degree relatives and healthy controls (NC). 2A) Partial correlations between choroid plexus volume and cognition (BACS composite score) and functioning (SFS total). 2B) Partial correlations between choroid plexus volume and total gray matter, lateral ventricle, hippocampus, cerebellum cortex, caudate and amygdala volume. Partial correlations were adjusted for age, sex, race, site. Imaging data was additionally adjusted for total intracranial volume. FDR corrected q-values.

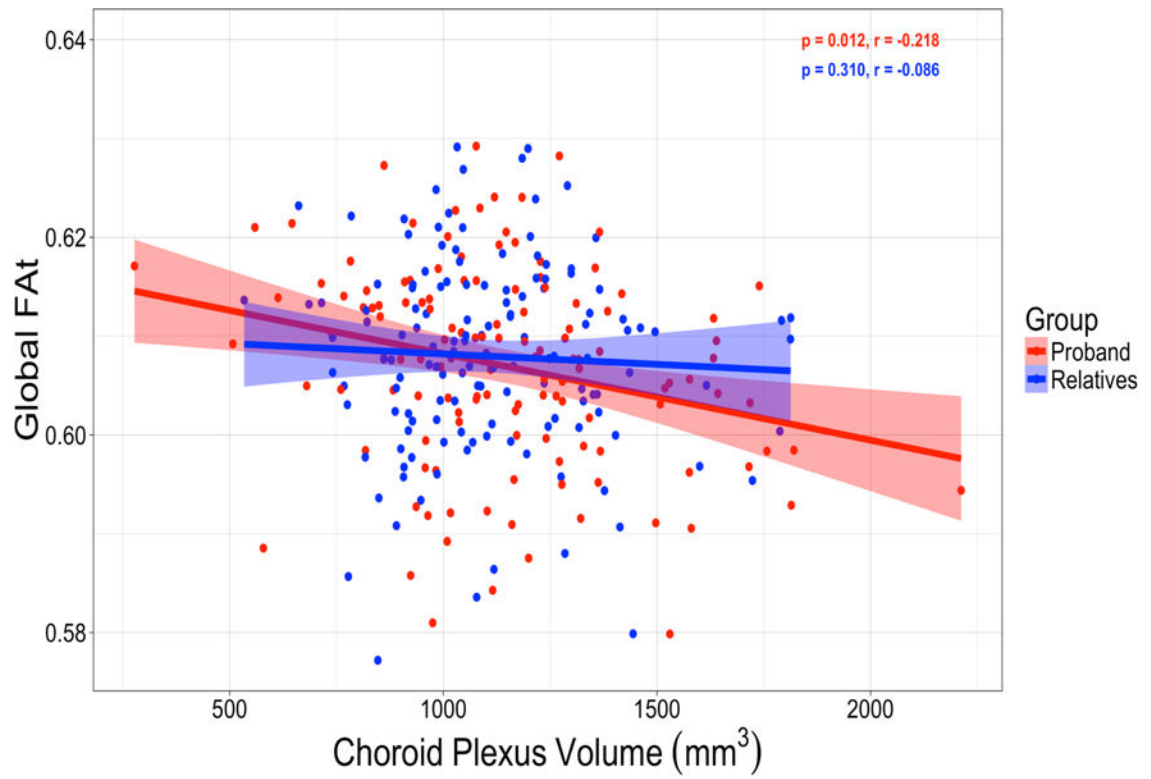


Figure 3. Choroid plexus volume correlations with free water corrected global fractional anisotropy (FA_t) in probands and relatives. Partial correlations were adjusted for age, sex, race, site. Choroid plexus volume was additionally adjusted for total intracranial volume.

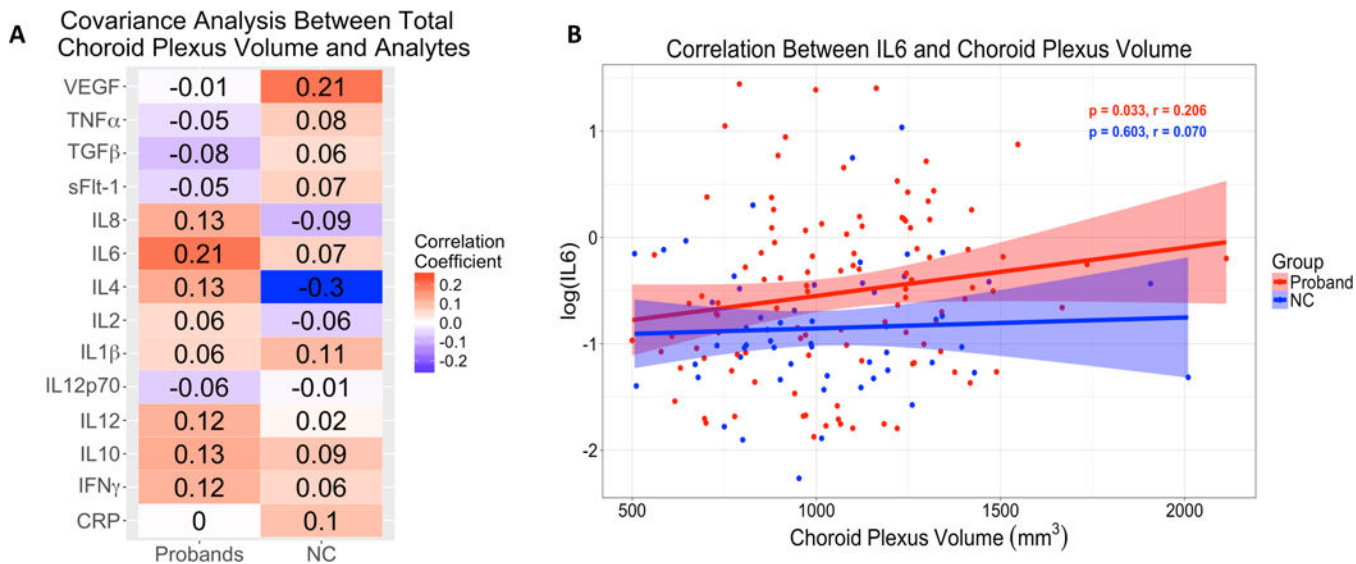


Figure 4. Choroid plexus volume partial correlations with analyte measures in probands and healthy controls (NC). 3A) Partial correlations between choroid plexus volume and analytes. 3B) Partial correlation between choroid plexus volume and log(IL6) in probands and NC. Partial correlations were adjusted for age, sex, and race and p-values FDR corrected for multiple comparisons. Imaging data was additionally adjusted for total intracranial volume and analyte data was additionally adjusted for sample storage days.

Table 1:

Sample Characteristics of the Comparisons between Probands, First Degree Relatives and Control Subjects

	NC (n=333)		Probands (n=554)		Relatives (n=522)		χ^2	p-value
	N		N		N			
Sex (Male/Female) ^a	149/184		267/287		158/364		39.3	<0.001
Race (AA/CA/OT) ^a	88/215/30		206/313/35		146/350/26		24.5	<0.001
Antipsychotic class (FGA/SGA/none)	-		48/406/90		-		-	-
	Mean	SD	Mean	SD	Mean	SD	F	p-value
Age (years) ^a	37.0	12.4	35.5	12.5	40.8	15.6	13.6	<0.001
Duration of Illness (years)	-	-	17.9	12.2	-	-	-	-
Age of onset (years)	-	-	17.6	7.7	-	-	-	-
PANSS Total Scores	-	-	62.9	16.9	-	-	-	-
Daily CPZ equivalents	-	-	446.9	390.5	-	-	-	-
ICV (mm ³)	1,431,124.5	191,440.9	143,5747.3	184,991.4	1,406,251.9	179,218.8	2.58	0.055

Notes: NC, normal controls; SD, standard deviation; AA, African American; OT, other; CA, Caucasian; NC, healthy control; FGA, first generation antipsychotics; SGA, second generation antipsychotic; CPZ, chlorpromazine; PANSS, Positive and Negative Symptoms Scale; ICV, intracranial volume

^a, p<0.05.