Title: Linking Choroid Plexus Enlargement with Plasma Analyte and Structural Phenotypes in Clinical High Risk for Psychosis: A Multisite Neuroimaging Study

Short Title: Choroid Plexus Enlargement in Clinical High Risk for Psychosis

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Abstract

Background: Choroid plexus (ChP) enlargement has been described in first-episode psychosis and psychosis spectrum disorders, but whether ChP enlargement occurs before disease onset is unknown. This study investigated whether ChP volume is enlarged in individuals with clinical high-risk (CHR) for psychosis and whether these changes are related to clinical, cortical, and plasma analyte measures.

Methods: Clinical and neuroimaging data from the North American Prodrome Longitudinal Study 2 (NAPLS2) was used for analysis. A total of 509 participants (169 controls, 340 CHR) were recruited across 8 sites. Conversion status was determined until 2-years of follow-up, with 36 patients developing psychosis. The lateral ventricle ChP was manually segmented from all available baseline brain scans. A subsample of 84 participants (31 controls, 53 CHR) had plasma analyte and neuroimaging data.

Results: Compared to controls, CHR overall (*d=0.22, p=0.017*) and converters *(d=0.21, p=0.041)* demonstrated higher ChP volumes, but not nonconverters. In CHR, greater ChP volume correlated with lower cortical *(r=-0.22, p<0.001)* and subcortical gray matter volume *(r=-0.21, p<0.001)*, total white matter volume *(r=-0.28,p<0.001),* and larger lateral ventricle volume *(r=0.63,p<0.001)*. In CHR, greater ChP volume, but not lateral ventricle volume, correlated with higher C3 *(r=0.39, p=0.005)* and TSH *(r=0.31, p=0.026),* and lower MMP7 *(r=-0.30, p=0.032)* and UMOD *(r=-0.33, p=0.019)*.

Conclusions and Relevance: CHR and converters to psychosis demonstrated significantly larger ChP volumes compared to controls. ChP enlargement was associated with cortical volume reduction and increased peripheral inflammatory markers. These findings suggest that the ChP may be a key biomarker in psychosis disease onset and conversion.

Main Text

Introduction:

The choroid plexus (ChP) projects into the four cerebral ventricles and is the principal source of cerebrospinal fluid (CSF). Together, the ChP and CSF play an important role in brain physiology[1,2], buoyancy[3], and homeostasis by providing physical, enzymatic, and immunological barriers to the brain[4]. Neuroimaging studies have observed ChP changes with aging[5–7] and across various neurodevelopmental[8–10] and brain disorders[11–13], suggesting that the ChP may play a key role in brain disorders. Despite growing evidence implicating the ChP in neurodevelopment and brain disorders, it has not been the focus of commonly used neuroimaging tools, which causes it to be poorly segmented, mislabeled, and incorrectly quantified[14]. Therefore, there is a critical need to elucidate the role of the ChP in brain disorders using more accurate segmentation of the ChP.

The earliest observations of ChP morphological changes in schizophrenia and bipolar disorders occurred in the early 20th century, where cystic formations, fibrosis, lipid deposits, and hypersecretory phenotypes were found in ChP epithelial cells, as well as endothelial cell degradation[15–17]. We previously reported on ChP enlargement in a large sample of patients with schizophrenia, schizoaffective, and psychotic bipolar disorder compared to healthy controls[18]. Larger ChP volume was associated with worse overall cognition, but no correlations with clinical measures were identified. A link between ChP volume and brain structure was established, with greater ChP volume relating to smaller gray matter and subcortical volume, larger ventricular volume, and lower white matter microstructure. Enlarged ChP volume correlated with higher peripheral levels of interleukin-6, suggesting that inflammation may play a role in ChP structural changes observed in psychosis and inflammation-meditated CSF hypersecretion[19,20]. These findings were replicated in a study in first-episode schizophrenia, where the greater ChP volume observed also correlated with higher allostatic load (indexed by subclinical cardiovascular,

metabolic, neuroendocrine, and immune markers)[21]. Another study reported larger ChP volume in schizophrenia patients with orofacial tardive dyskinesia and identified associations with elevated N-methyl-D-aspartate receptor antibody levels[22]. Taken together, these results suggest that the ChP may be an important structure in mechanisms underlying psychosis pathology. However, no studies to date have investigated ChP volumes in a population at clinical high risk (CHR) for psychosis to determine whether ChP enlargement is associated with future psychosis risk.

The results from these neuroimaging studies are promising; however, the use of FreeSurfer for ChP segmentation limits their interpretation, primarily due to poor ChP segmentation by FreeSurfer[14]. Recently, three tools have been developed to provide better ChP parcellation: Gaussian Mixture Model (GMM; Alzheimer's)[23], an optimized 3D U-Net[24] (aging healthy individuals), and an axial multi-layer perceptron (Axial-MLP 8)[25]. While robust, each technique only provides adequate segmentation performance, reflected in average Dice Coefficients (DC) of 64 for GMM, 71 for Axial-MLP8, and 73 for 3D U-Net. Therefore, in this study, we aim to analyze ChP volume in individuals at CHR for psychosis using manually segmented lateral ventricle ChP from the North American Prodrome Longitudinal Study 2 (NAPLS2) and will compare these manually-segmented values to two techniques previously used to study ChP volume in neuropsychiatric disorders: FreeSurfer 6.0 and GMM. We further aim to understand whether greater ChP volume is related to clinical, neuroimaging, and plasma analyte measures. We hypothesized that the CHR group will demonstrate ChP enlargement compared to healthy controls (HC) and that converters to psychosis will have higher volumes. Finally, we hypothesized that greater ChP volumes in CHR would be associated with worse cognition, global brain volume reduction, and higher plasma analyte levels.

Methods:

Participants

Participants were part of NAPLS2, a prospective multisite study analyzing psychosis predictors in individuals 12-35 years of age meeting Criteria of Psychosis Risk Syndromes[26]. Institutional Review Board approval was obtained from all sites[27]. Participants included 521 individuals (175 HC and 346 CHR) who had completed T1 MRI scans. Each participant provided written consent and parents/guardians provided consent for minors with minors providing assent. Exclusion criteria included current or lifetime Axis I psychotic disorder, IQ<70, past history of a central nervous system disorder, substance dependence within the past 6 months, and prodromal symptoms caused by an Axis I disorders. Non-psychotic DSM-IV disorders were not exclusionary (e.g. substance abuse disorder, anxiety disorders, or Axis II disorders) if they did not account for psychosis-risk symptoms. Exclusionary criteria for HC included meeting psychosis-risk syndrome criteria, any current or past psychotic disorder or Cluster A personality disorder, first-degree family history of any psychotic disorder or any disorder involving psychotic symptoms, and currently using psychotropic medications. Symptoms were assessed using the Scale of Psychosis-risk Symptoms (SOPS)[27,28]. The Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS)[29–31] and Global Assessment of Functioning (GAF)[32] measures were gathered to evaluate cognition and functioning, respectively. Social cognition was tested using The Awareness of Social Inference Test (TASIT)[33]. A questionnaire documenting trauma from before the age of 16 was collected. Conversion status was determined at 12-month-follow-up or at the point of conversion to psychosis for either a psychotic illness or bipolar disorder (bipolar 1/2, cyclothymic, or not-otherwise-specified). Substance use status was categorized by alcohol, amphetamine, cannabis, cocaine, hallucinogen, or polysubstance use. Illness duration categories (short or long) were determined by median split (30.9 weeks). Antipsychotic status and average daily chlorpromazine (CPZ) equivalents were collected[34]. One HC was dropped due to conversion to psychosis. Lastly, 5 participants were dropped due to missing diagnostic information.

MRI data

Subjects had baseline MRI scans that were free of visually detectable artifacts. A detailed explanation of scanner parameters and site harmonization was detailed previously[35]. Five sites used Siemens 3T with a 12-channel head coil (Emory, Harvard, Yale, University of California Los Angeles, and University of North Carolina) and 3 used GE 3T with an 8-channel head coil (Zucker Hillside, University of California San Diego, and University of Calgary). Images were acquired in the sagittal plane with a 1x1x1.2mm resolution. Siemens devices used an MPRAGE sequence with a 256x240x176mm field of view, TR/TE/T1=2300/2.91/900ms, and a 9-degree flip angle. GE scanners used an IR-SPGR sequence with a 26cm field of view, TR/TE/TI=7.0/minimum full/400ms, and an 8-degree flip angle.

Choroid plexus segmentation

T_1-MPRAGE images were processed through FreeSurfer v6.0[36]. Upon visual inspection, FreeSurfer lateral ventricle ChP maps were found to segment ~50% of the structure (Figure 1A,D,G,J). Thus, a Gaussian Mixture Model (GMM), previously developed for ChP analysis in Alzheimer's disease, was used to segment ChP[23]. However, GMM ChP parcellations were found to be inaccurate (Figure 1B,E,H,K) and we decided to manually-segment the ChP for all scans. 3D Slicer v4.11 was used for manual segmentation by 8 trained raters (IA, DB, SG, RH, SP, NR, AZ) in a first pass. In the second pass, brains were given to a new rater for further checking and editing, and a final evaluation was done from an expert rater (DB) to ensure cohesion of manual segmentation across all raters. DB was trained by PL, a senior neuropsychiatrist with 8 years of clinical and image processing experience. The trigonum collaterale was used as a reliable starting point for segmentation. Manual segmentation started in the axial>sagittal>coronal views to ensure the entirety of the ChP was captured and that voxels from surrounding brain structures (e.g. fornix, hippocampus, corpus collosum, and thalamus) were excluded. A 3D inspection was performed at the final stage to ensure proper

overall segmentation (Figure 1A-C). Third and fourth ventricle ChP were excluded to better compare our segmentation results with FreeSurfer and GMM, both of which only segment lateral ventricle ChP. ChP volume measures were extracted using 'fslstats' (FMRIB Software Library, v6.0). FreeSurfer was used to extract intracranial volume (ICV), lateral ventricle volume (LVV), total and subcortical gray matter volumes (GMV), and total white matter volume (WMV). Cortical measures greater than 4 standard deviations (SD) were removed (N=8) and those between 3-4 SD (N=21) were winsorized to the 3rd SD. Manual segmentation was considered the gold standard with respect to FreeSurfer 6.0 and GMM segmentations of the lateral ventricle ChP.

Plasma analyte collection

84 participants (33 HC and 51 CHR) had both MRI and plasma analyte data. A comprehensive detail of blood collection/assay has been provided previously[37]. In brief, blood was collected at baseline, processed within 120min and stored at -80°C. 185 analytes were immunoassayed blind to the subject's clinical status. 44 analytes were previously excluded due to medication or substance use confounds[37]. 13 analytes were not detected in >25% of subjects and were excluded (Supplementary Table 1). CHR vs HC comparisons were performed on the remaining 185 analytes and significant analytes were used for subsequent analyses.

Statistical Analysis

Sociodemographic variables were compared between groups via Chi-square or analysis of variance (ANOVA) tests for categorical and continuous data, respectively. ANOVAs were performed to test the moderating effects of age, sex, race, site, ICV, and total GMV on manually-segmented ChP volume. Significant moderators ($p<0.05$) were used as covariates in ChP analysis and included age, sex, race, and site (Supplementary Table 2). ICV was used as an additional covariate for ChP measures. DC[38] and absolute intraclass correlation[39] (ICC) were

used to measure the accuracy and reliability of ChP segmentation between FreeSurfer, GMM, and manual segmentation. DC is a measure of the number of overlapping voxels segmented as ChP in two masks with values ranging from 0-100, where 0 designates no overlap and 100 reflects total overlap. Absolute ICC is a measure of agreement between two measurements and ranges from 0 to 1 (1=high reliability). General linear models, controlling for confounding variables, were used for group contrasts between CHR and HC. Post hoc comparisons examining conversion (converters vs non-converters), antipsychotic, duration (short vs long), and substance use status were performed. Effect sizes were calculated using Cohen's d. To analyze whether ChP volume results were impacted by LVV or GMV, ChP group contrasts were performed using 1) LVV and 2) LVV and GMV in place of ICV as a covariate. Partial Spearman correlations were used to analyze associations between ChP volume and clinical (n= 10), brain (n= 4), and analyte measures (n=15), and calculated p-values were corrected for multiple comparisons using the false discovery rate (FDR) method (q-values)[40]. All statistical analyses were performed using R statistical software (version 3.5.1).

Results:

Demographics

The final sample included 340 CHR and 169 HC (Table 1). HC and CHR demonstrated no race differences, but differed for age *(p=0.003)*, sex *(p=0.025)*, and site *(p=0.006)*. CHR had higher rates of substance use disorder (*p=0.004)*, SOPS (total, positive, negative, disorganization) and trauma scores *(p<0.001)*. CHR had lower GAF, MATRICS, and TASIT scores *(p<0.001)*. 105 (30%) CHR were on a first- or second-generation antipsychotic, with an average daily chlorpromazine dosage of 187.8mg. In CHR with available data on conversion status (n=277), 36 (13%) converted to psychosis.

Accuracy and reliability of ChP segmentation

Compared to manual segmentation, FreeSurfer *(DC=29; left ICC=0.41, p<0.001; right ICC=0.44, p<0.001; bilateral ICC=0.44, p<0.001;* Figure 1N,M) and GMM *(DC=67; left ICC=0.45, p<0.001; right DC=0.51, p<0.001; bilateral ICC=0.53, p<0.001)* demonstrated poor accuracy and reliability. Compared to FreeSurfer, GMM demonstrated significantly higher accuracy (*ΔDC=0.37, p<0.001*). Thus, manually segmented ChP volumes were used for primary analyses.

ChP differences

CHR demonstrated higher ChP volume compared to HC *(left: d=0.22, p=0.02, q=0.02; right: d=0.22, p=0.02, q=0.02; bilateral: d=0.22, p=0.017, q=0.02;* Figure 2A, Supplementary Table 3). This effect did not hold after controlling for LVV or LVV+GMV (Supplementary Table 3). For group differences using FreeSurfer or GMM ChP measures see Supplementary Table 3. In CHR, post hoc comparisons were performed using conversion (36 converters, 231 non-converters), antipsychotic (105 antipsychotics, 241 no antipsychotics), illness duration (155 short, 156 long), and substance use statuses (24 substance use, 322 no substance use; Supplementary Table 4). Compared to HC, converters had higher ChP volumes *(d=0.15, p=0.021*, Figure 2B; Supplementary Table 5). CHR not on antipsychotics demonstrated larger ChP compared to HC *(d=0.21, p=0.041)*, while CHR on antipsychotics had larger ChP compared to those not on antipsychotics *(d=0.041, p=0.035;* Figure 2C). CHR with longer illness durations had larger ChP compared to HC *(d=0.18, p=0.008;* Figure 2D). Lastly, CHR both with and without a history of substance abuse had significantly higher ChP volumes compared to HC *(no-substance use d=0.20, p=0.035; substance use: d=0.56, p=0.015;* Figure 2E).

Clinical correlations

No significant correlations were observed between ChP volume and SOPS, global functioning, MATRICS, trauma, or social cognitive scores in the overall, CHR or HC groups (Supplementary Table 6). In CHR, no associations were noted between ChP volume and illness duration or CPZ equivalence.

Neuroimaging correlations

In CHR, larger ChP was associated with lower total GMV *(r=-0.22, p<0.001, q<0.001)*, subcortical GMV *(d=-0.21, p<0.001, q<0.001)*, and WMV *(r=-0.28, p<0.001, q<0.001),* as well as with higher LVV *(r=0.63, p<0.001, q<0.001;* Figure 3, Supplementary Table 7). HC demonstrated significant correlations between higher ChP and lower WMV *(r=-0.27, p<0.001, q<0.001)* and higher LVV *(r=0.66, p<0.001, q<0.001)*.

Exploratory plasma analyte correlations

There were no sociodemographic differences between HC and CHR in the subset of participants with both MRI and analyte data (Supplementary Table 8). In CHR, greater ChP volume was associated with higher levels of thyroid stimulating hormone (TSH; *r=0.39, p=0.004*) and lower levels of alpha-2 macroglobulin (A2M; *r=-0.29, p=0.037*), lymphocyte secreted protein I-309 (CCL1; *r=-0.42, p=0.002*), myeloperoxidase (MPO; *r=-0.39, p=0.006*), and tissue inhibitor of metalloproteinases-1 (TIMP-1; *r=-0.29, p=0.041;* Figure 4). Non-converters demonstrated negative relationships between ChP volume and peripheral levels of A2M *(r=-0.43, p=0.01)*, CCL1*(r=-0.43, p=0.01)*, MPO *(r=-0.43, p=0.01)*, TIMP-1 *(r=-0.43, p=0.01)*, and vascular cell adhesion molecule-1 (VCAM-1; *r=-0.43, p=0.01*). Interestingly, converters showed strong correlations between enlarged ChP volume and greater peripheral AXL receptor tyrosine kinase (AXL; *r=-0.43, p=0.01*), creatine kinase-MB (CKM; *r=-0.43, p=0.01*), epidermal growth factor receptor (EGFR; *r=-0.43, p=0.01*), glutathione S-transferase alpha 1 (GSTA1; *r=-0.43, p=0.01*), intracellular adhesion molecule-1 (ICAM-1; *r=-0.43, p=0.01*), myoglobin (MB; *r=-0.43, p=0.01*),

and E-selectin (SELE; *r=-0.43, p=0.01*) levels. In controls, ChP volume was associated with higher placental growth factor (PGF; *r=0.42, p=0.048*) and lower endothelin-1 (EDN1; *r=-0.55, p=0.046*), interleukin-3 (IL-3; *r=-0.36, p=0.041*) and interleukin-4 (IL-4; *r=-0.59, p=0.004*).

Discussion:

Our study demonstrated that patients with CHR, who converted to psychosis, with longer illness durations, or on antipsychotics had larger ChP volume compared to HC. While no clinical correlations were observed in CHR, enlarged ChP was associated with lower cortical and subcortical volumes, and larger LVV. Larger ChP was also associated with elevated complement C3 and TSH levels and lower MMP7 and UMOD levels. FreeSurfer and GMM demonstrated poor accuracy/reliability for ChP segmentation compared to manual segmentation. Together, these results suggest that the ChP may be an important risk and treatment biomarker for CHR individuals.

These results extend upon prior findings of lateral ventricle ChP enlargement in first-episode schizophrenia[21] and chronic psychosis[18] using a more accurate method for ChP segmentation. ChP enlargement has been reported in other neuropsychiatric disorders, such as Alzheimer's[12], multiple sclerosis (MS)[41,42], neuromyelitis optica[41], and major depressive disorder[13]. Normal size criterion for the ChP does not exist to compare our findings to, but one study in children[5] (0-16 years) and two studies in adults (18-94 years)[6,7] have attempted to do this. However, these studies have been limited by small sample sizes, measurement types (thickness vs volume), neuroimaging modality (MRI vs ultrasound), narrow age categories (mostly older adults), and use of less accurate ChP segmentation algorithms, which make it challenging to understand the role of ChP morphology in psychotic disorders.

What ChP enlargement might mean for patients with psychosis has yet to be determined, but recent studies have shed light on this matter. For example, Lizano et al. (2019)[18] observed

relationships between ChP enlargement and larger LVV and lower total GMV in psychotic disorders. In MS, ChP enlargement was associated with higher LVV, greater WM lesions, lower brain volume, and normal-appearing WMV[42]. In depression, researchers found that ChP enlargement correlated with markers of central inflammation, namely greater mitochondrial translocator protein (TSPO) expression within the anterior cingulate, prefrontal, and insular cortices[13]. ChP enlargement was also associated with higher neuroinflammation in MS, reflected by greater ^{18}F-DPA-714 binding in the thalamus[42]. The ChP of MS patients demonstrated greater TSPO expression compared to controls, suggesting an increased presence of immune cells within the ChP epithelium. Similarly, greater gadolinium enhancement of lateral and 4th ventricle ChP in MS was identified suggesting a potential increase in ChP stromal capillary permeability[41]. These studies suggest that ChP enlargement is associated with inflammatory and microvascular changes within the ChP itself, as well as other parenchymal areas.

An additional gap in the literature pertains to the effects of circulating peripheral analytes on ChP morphology. Previous work has demonstrated associations between ChP enlargement and higher peripheral IL6[18] in those with chronic psychosis and with greater allostatic load in first-episode SZ[21]. We could not examine IL6 in our exploratory correlational analysis since it did not survive our quality control. However, we found that enlarged ChP in CHR correlated with higher TSH and lower A2M, CCL1, MPO and TIMP-1 levels. Patients with first-episode SZ have been found to have significantly lower peripheral TSH levels compared to patients with multi-episode SZ, who demonstrated significantly higher TSH levels albeit with a significant degree of heterogeneity[43]. In our sample, CHR on antipsychotics had significantly higher TSH levels (mean TSH=1.95, SD=0.78) compared to CHR not on antipsychotics (mean TSH=1.41, SD=0.7; *p=0.02, d=0.75)* which may reflect a potential hypothyroidism caused by antipsychotic usage[44]. Further studies are necessary to better understand the relationship between TSH levels and antipsychotic usage as well as between elevated TSH levels and enlarged ChP. Reductions in

serum A2M have been observed in individuals at high-risk for SZ as well as in patients with SZ[45,46]. A2M is a broad protease inhibitor as well as a cytokine transporter and can be thought of as able to inhibit inflammatory cytokines and cascades[47], which supports its observed inverse association with ChP volume in CHR. In contrast, CCL1 and MPO are analytes associated with pro-inflammatory processes and are secreted by immune cells and expressed by neutrophil granulocytes, respectively. We expected both to have positive relationships with ChP volume in CHR, linking peripheral and central inflammation. In mice, Ito et al. (2019)[48] linked CCL1, intraventricular not serum, to regulatory T-cell infiltration of the brain after stroke. Elevated serum MPO has been described in multiple sclerosis[49], depression[50], and schizophrenia[51]. Interestingly, Baranyi et al. (2022)[52] described lower MPO levels in patients with acute myocardial infarction (AMI) induced depression compared to AMI patients that did not develop depression. This suggests that there may be an interaction occurring between inflammatory and neuropsychiatric states with regards to MPO serum levels, but further research is needed. Lastly, TIMP-1 acts as an inhibitor to matrix metalloproteinases and is key in maintaining the composition of the extracellular matrix. While elevated serum TIMP-1 and MMP9 have been described in SZ[53], TIMP-1 has also been shown to play a protective role in blood-brain-barrier (BBB) integrity after damage via a mechanism independent of matrix metalloproteinase activity[54]. More research studying the mechanisms of TIMP-1 in SZ are needed to better elucidate the role of TIMP-1 in disease and protective states.

In conclusion, our results suggest that the ChP is a biomarker of particular interest for neurodevelopment and CHR for psychosis. Strengths of this study include the use of manually-segmented ChP volume in the largest sample size of CHR patients. Limitations include 1) a sample size for examining ChP to peripheral analyte relationships, 2) lack of 3rd/4th ventricle ChP segmentation given their proximity to important brain areas (hippocampus and cerebellum), and 3) cross-sectional neuroimaging design. Future studies should focus on these remaining gaps to would allow for a more compressive understanding of ChP morphology in psychosis.

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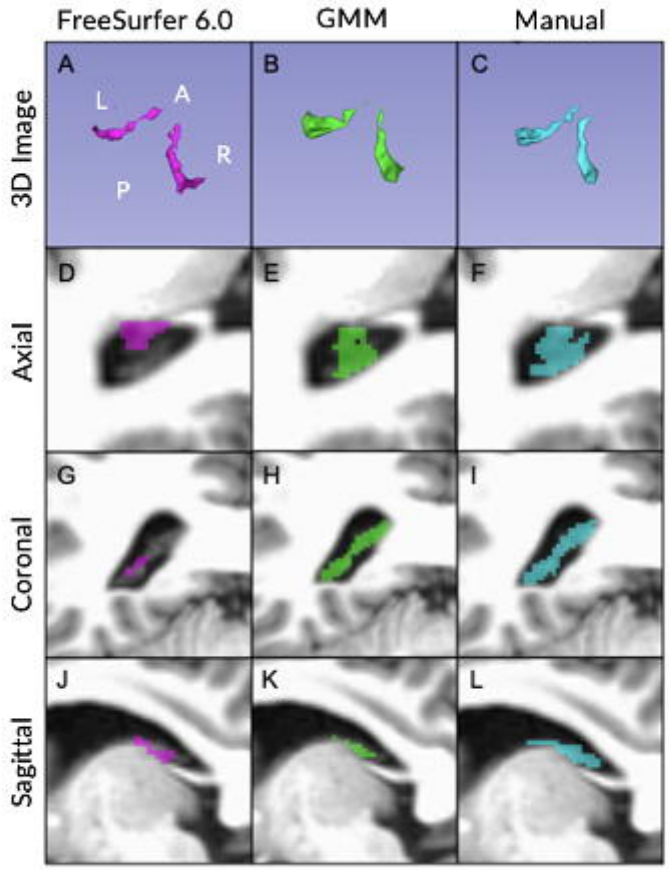
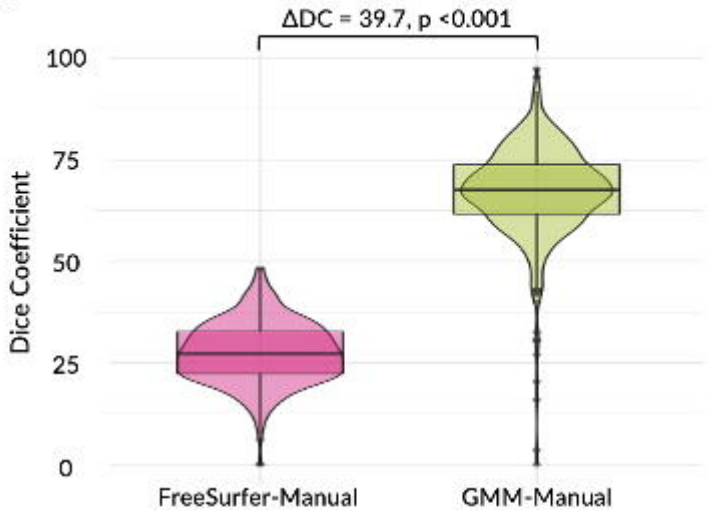
Figure 1. Schematic showing differences in choroid plexus segmentation between FreeSurfer 6.0 (Figures 1A, 1D, 1G, and 1J), Gaussian Mixture Model (Figures 1B, 1E, 1H, and 1K), and manual segmentation (Figures 1C, 1F, 1I, and 1L). White letters stand for: "A", anterior; "P", posterior"; "R", right; "L", left. Panel M demonstrates the difference in segmentation accuracy, quantified using Dice coefficients. Panel N enumerates intra-class correlation values across the three segmentation techniques.



M



N

ICC between choroid plexus segmentation techniques.

	FreeSurfer-Manual		*GMM-Manual*		*FreeSurfer-GMM*	
	ICC	*p*	*ICC*	*p*	*ICC*	*p*
Left	0.41	**<0.001**	0.45	**<0.001**	0.34	**<0.001**
Right	0.44	**<0.001**	0.51	**<0.001**	0.45	**<0.001**
Bilateral	0.44	**<0.001**	0.53	**<0.001**	0.48	**<0.001**

GMM, Gaussian mixture model; ICC, intra-class correlations. Note: Raw choroid plexus measures from each segmentation technique were used to calculate the Sørensen-Dice coefficients and ICC. Statistically significant measures are denoted in bold.

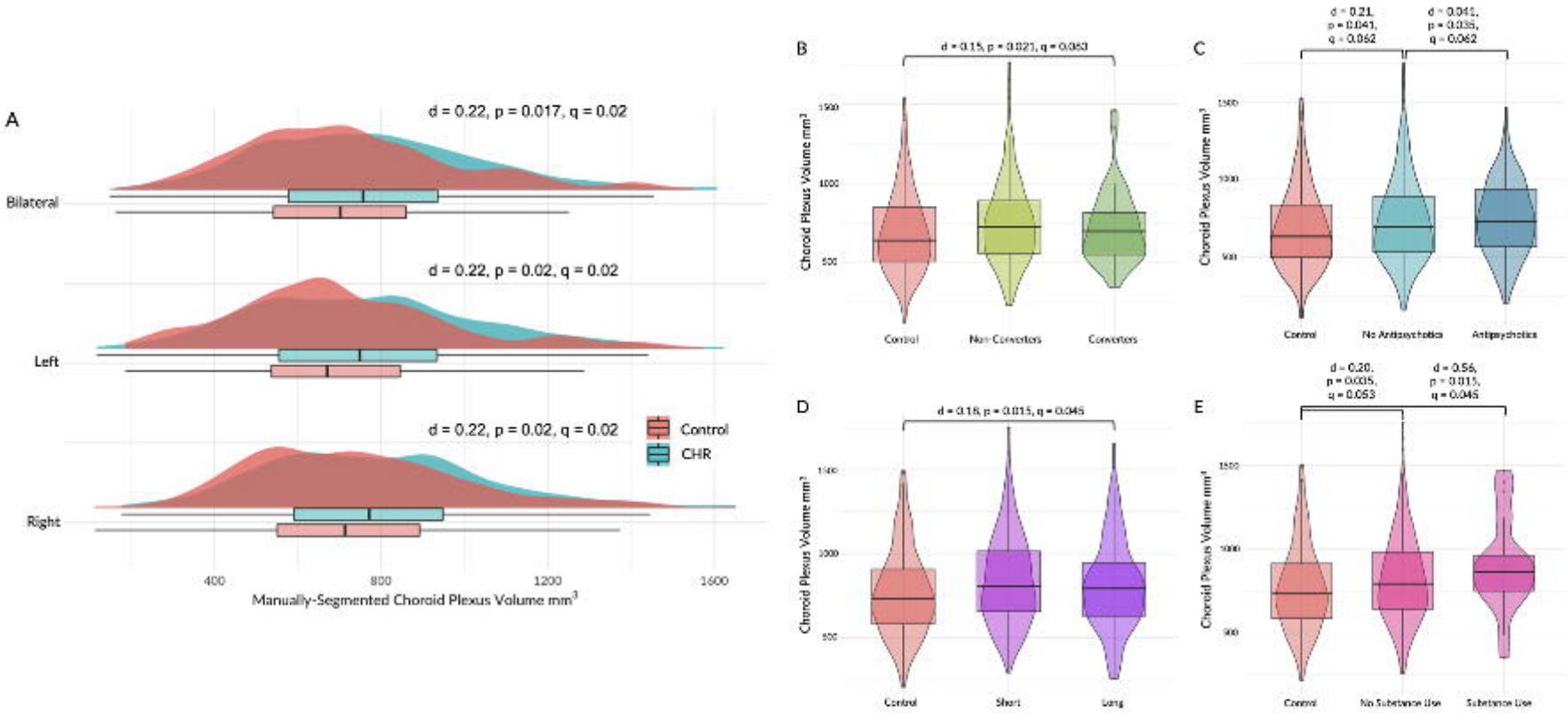
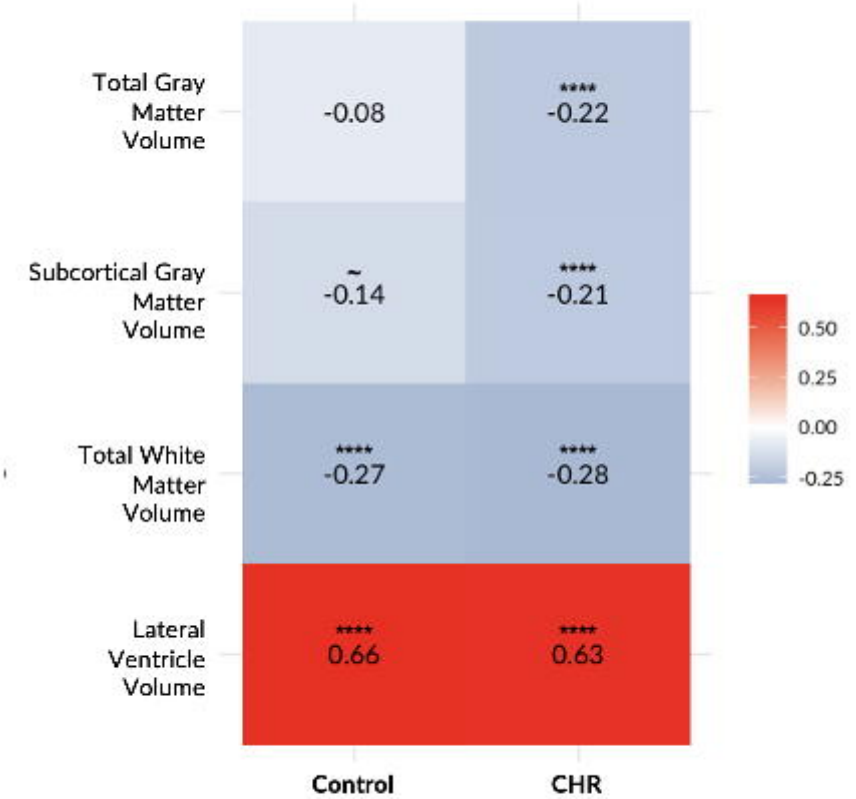


Figure 2. Panel A denotes diagnostic group differences between controls and CHR. Choroid plexus volume was corrected for age, sex, race, site number, and intracranial volume. Panels B-E demonstrate subgroup differences between controls and (B) non-converters and converters, (C) individuals on and not on antipsychotics, (D) individuals with short and long illness durations, and (E) individuals with and without a history of substance use. Note: ChP measures were covaried for age, sex, race, site number, and total intracranial volume.

Figure 3. Choroid plexus volume correlations with cortical measures.



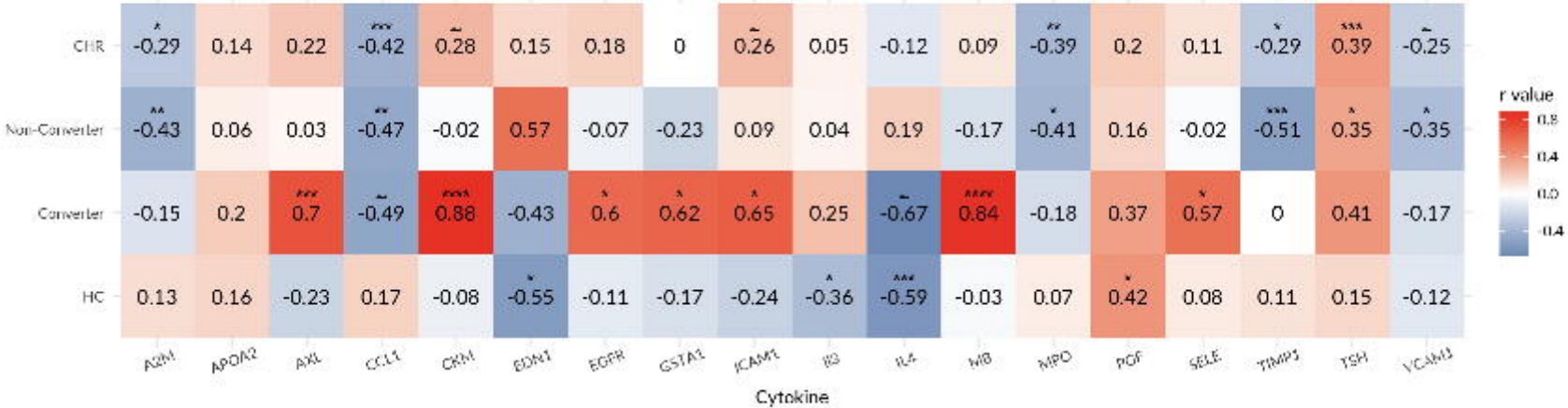


Figure 4. Choroid plexus correlations with analyte measures within CHR, non-converters, converters, and HC.

Table 1. Clinical and demographics information.

Variable	HC (n=169)	CHR (n=340)	Test Stat (χ^2,F)	p
Age (years)	**20.1 (4.8)**	**18.9 (4.1)**	**8.92**	**0.003**
Sex (Female/Male)	**87/82**	**138/202**	**5**	**0.025**
Race (CA/OT)	93/76	192/147	0.062	0.81
Site Number (1-8)	**20/16/26/20/23/16/23/25**	**38/45/23/37/55/33/79/30**	**19.6**	**0.006**
Antipsychotic Status (Yes/No)	-	241/105	-	-
CPZ Equivalent	-	187.8 (216.6)	-	-
Converter/Non-Converter	-	36/231	-	-
Substance Use Disorder (Yes/No)	**1/168**	**24/332**	**8.25**	**0.004**
Duration of Illness (weeks)	-	51.4 (75.7)	-	-
SOPS Total Score	4.29 (5.99)	37.6 (13.0)	**1010**	**<0.001**
SOPS Positive	0.94 (1.57)	12.0 (4.2)	**1110**	**<0.001**
SOPS Negative	1.43 (2.36)	11.6 (6.2)	**416**	**<0.001**
SOPS Disorganization	0.62 (1.15)	5.19 (3.3)	**307**	**<0.001**
GAF	84.12 (10.51)	48.9 (11.4)	**1140**	**<0.001**
MATRICS Composite	432.5 (65.1)	391.2 (71.0)	**36.8**	**<0.001**
Documentation of Trauma	5.56 (2.5)	7.41 (2.7)	**56.3**	**<0.001**
Social Cognition (TASIT)	54.7 (5.4)	52.9 (6.0)	**10.2**	**0.002**

HC, healthy controls; CA, Caucasian; OT, other; CPZ, chlorpromazine; SOPS, Scale of Prodromal Symptoms; GAF, Global Assessment of Functioning; MATRICS, Measurement and Treatment Research to Improve Cognition in Schizophrenia; BACS, Brief Assessment of Cognition in Schizophrenia; TASIT, The Awareness of Social Inference Test. **Note:** Sites 1-8 are as follows: University of California Los Angeles, Emory, Harvard, Zucker Hillside Hospital, University of North Carolina, University of California San Diego, University of Calgary, and Yale. Statistical significance is denoted in bold.