Received: 5 May 2022 | Revised: 13 December 2022 | Accepted: 21 January 2023

DOI: 10.1002/hbm.26224

RESEARCH ARTICLE

WILEY

A preliminary choroid plexus volumetric study in individuals with psychosis

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Funding information
National Institutes of Health (NIH), Grant/Award Numbers: 5U01MH109977-04,

Abstract

The choroid plexus (ChP) is part of the blood-cerebrospinal fluid barrier, regulating brain homeostasis and the brain's response to peripheral events. Its upregulation and enlargement are considered essential in psychosis. However, the timing of the ChP enlargement has not been established. This study introduces a novel magnetic

Olcay Senay and Magdalena Seethaler contributed equally.

Johanna Seitz-Holland and Marek Kubicki contributed equally.

K24MH110807, R01MH102377; core facility MAFIL supported by the Czech-BioImaging large RI project, Grant/Award Number: LM2018129; Harvard Medical School Livingston Fellowship Award; Young Investigator Grant sponsored by Mary and John Osterhaus and the Brain & Behavior Research Foundation; Evangelische Studienstiftung Villigst

resonance imaging-based segmentation method to examine ChP volumes in two cohorts of individuals with psychosis. The first sample consists of 41 individuals with early course psychosis (mean duration of illness = 1.78 years) and 30 healthy individuals. The second sample consists of 30 individuals with chronic psychosis (mean duration of illness = 7.96 years) and 34 healthy individuals. We utilized manual segmentation to measure ChP volumes. We applied ANCOVAs to compare normalized ChP volumes between groups and partial correlations to investigate the relationship between ChP, LV volumes, and clinical characteristics. Our segmentation demonstrated good reliability (.87). We further showed a significant ChP volume increase in early psychosis (left: $p < .00010$, right: $p < .00010$) and a significant positive correlation between higher ChP and higher LV volumes in chronic psychosis (left: $r = .54$, $p = .0030$, right: $r = .68$; $p < .0010$). Our study suggests that ChP enlargement may be a marker of acute response around disease onset. It might also play a modulatory role in the chronic enlargement of lateral ventricles, often reported in psychosis. Future longitudinal studies should investigate the dynamics of ChP enlargement as a promising marker for novel therapeutic strategies.

KEYWORDS
cerebrospinal fluid, manual segmentation, neuroinflammation, perivascular space, schizophrenia, ventricle

1 | INTRODUCTION

Psychosis constitutes a group of severe psychiatric disorders that affect ~5% of the world population and can significantly impact afflicted individuals, families, and society (Gerlinger et al., 2013; van Os et al., 2009). Thus, an important focus of research is understanding the pathophysiology of psychosis in order to develop novel diagnostic, prognostic, and treatment strategies.

While the importance of the choroid plexus (ChP) for the pathophysiology of psychosis has been suggested since the 1970s (Rudin, 1979, 1980), it has only recently attracted the attention of clinical neuroscientists as a potential marker for diagnosis, prognosis, and treatment. The ChP represents the vital part of the blood-cerebrospinal fluid (CSF) barrier, formed by an epithelial cell monolayer and a stromal component located in the lateral, third, and fourth ventricles (Demeestere et al., 2015). The ChP plays a crucial role in maintaining brain homeostasis, given its barrier and secretory functions. It provides structural support for the brain, produces most of the CSF, and secrets various endocrine products, including serotonin, vasopressin, transthyretin, growth factors, carriers, and chemokines (Alshehri et al., 2015; Brown et al., 2004; Szmydynger-Chodobska et al., 2009; Turner et al., 2014). As the blood-CSF barrier constitutes the main interface between the periphery and central nervous system, the ChP is also critical for brain development. Furthermore, it assists in eliminating toxins, provides protection against oxidative stress, and regulates the immunological crosstalk between peripheral and central inflammation (Marques et al., 2009). Specifically, the ChP responds to peripheral inflammatory signals by producing central pro-inflammatory cytokines and modulating immune cells' transmigration into the brain (Demeestere et al., 2015; Mortazavi et al., 2014).

Significantly, structural and functional disruptions of the ChP have been related to abnormal brain development, chronic stress, and aging in animals (Imura & Sato, 2008; Lowe & Wyrobek, 2012; Murthy et al., 2019; Sathyanesan et al., 2012), as well as several disorders in humans, including neuroinflammatory and septic conditions (Goldim et al., 2019; Rudin, 1980), neurodevelopmental and mood disorders (Devorak et al., 2015; McCann et al., 2021; Murck et al., 2021; Ricigliano et al., 2021), and psychosis (Demeestere et al., 2015; Marinescu et al., 2013). Indeed, for individuals with psychosis, postmortem studies report increased pro-inflammatory gene expression in the ChP (Kim et al., 2016). Additionally, two case reports describe an association between a tumorous increase of the ChP and psychotic symptoms, with symptom remission following tumor resection (Arasappa et al., 2013; Carson et al., 1997).

While lateral ventricle (LV) enlargements are a hallmark finding in psychosis (Fannon et al., 2000; Sanfilipo et al., 2000; Shenton et al., 2001; Silverman et al., 1998), computed tomography (CT) studies identified an association between the presence and size of ChP calcification in the LV and symptom severity in psychosis (Bersani et al., 1999; Marinescu et al., 2013; Sandyk, 1993). Furthermore, two magnetic resonance imaging (MRI) studies reported enlarged ChP volume in individuals with psychosis compared with healthy individuals (Lizano et al., 2019; Zhou et al., 2020). The first study compared individuals across the psychosis spectrum with first-degree relatives and healthy individuals and described enlarged ChP volumes in individuals with psychosis related to higher peripheral pro-inflammatory interleukin-6 (Lizano et al., 2019). The second study focused on individuals with a first-episode diagnosis of schizophrenia and found enlarged ChP volumes linked to increased allostatic load. In

line with earlier theories on the pathophysiology of psychosis (Feigenson et al., 2014; Weinberger, 1995), both studies concluded that enlarged ChP volume might be a marker of inflammatory brain response related to psychosis. Of note, blood, clinical, and imaging studies found evidence for peripheral inflammation, as well as an acute, potentially neuroinflammatory brain response around the onset of psychosis (Bustan et al., 2018; Fillman et al., 2013; Lyall et al., 2018; Pasternak et al., 2012; Pasternak et al., 2015; Petrikis et al., 2015; van Berckel et al., 2008).

Here, we aim to extend previous work on the role of ChP volumes in psychosis. Given its size, shape, and location, it is difficult to identify the ChP volume utilizing automatic methods (Tadayon et al., 2020). We, therefore, developed and validated a manual segmentation method for the ChP. We then applied this method to two independent cohorts: (1) 41 individuals with early course psychosis (mean duration of illness = 1.78 years) and 30 matched healthy individuals, and (2) 30 individuals with chronic psychosis (mean duration of illness n = 7.96 years) and 34 matched healthy individuals. We tested whether or not we could replicate ChP enlargements in psychosis using more accurate manual segmentation. We also investigated how ChP volumes relate to disease chronicity and associate with LV volumes in early versus chronic psychosis. Based on previous studies that suggested neuroinflammation around psychosis onset (Feigenson et al., 2014; Najjar et al., 2013; Najjar & Pearlman, 2015; Pasternak et al., 2012; Upthegrove et al., 2014) and the notion that the ChP enlargements might indicate neuroinflammation, we hypothesized that ChP enlargement would be more prominent in early course psychosis compared with more chronic stages.

2 | MATERIALS AND METHODS

We utilized two independent data sets for the study, and data processing was performed in parallel using the same methods and processing pipelines. We opted for this approach to examine individuals from different studies at different stages of the disorder. Data set #1 comprised 41 individuals with early course psychosis and 30 matched healthy individuals (HC) recruited by the Human Connectome Project at the Brigham and Women's Hospital. Please note that while the Human Connectome Project is a much larger, multisite study, we limited analyses to individuals that were collected at Brigham and Women's Hospital for the present study. Data set #2 comprised 30 individuals with chronic psychosis and 34 HC, recruited at the Department of Psychiatry at University Hospital Brno, Brno, Czech Republic. All participants provided informed written consent, and the review boards of Harvard Medical School and the University Hospital Brno approved the study.

2.1 | Data collection

While all individuals with psychosis in data set #2 were diagnosed with schizophrenia, data set #1 included individuals diagnosed with any DSM-5 non-affective or affective psychosis. We, therefore, opted to use the term "individuals with psychosis" throughout the manuscript. However, in an additional analysis, we only included individuals diagnosed with schizophrenia from data set # 1.

2.1.1 | Data set #1: Early course psychosis

Individuals with psychosis were diagnosed with a DSM-5 non-affective or affective psychosis defined by the Structured Clinical Interview for DSM-5-Research version (SCID-5-RV) or DSM-5-RV interview (First, 2015). Duration of illness was determined via the SCID interview, and duration of illness longer than 5 years was considered an exclusion criterion. The Positive and Negative Syndrome Scale (PANSS) was administered to determine symptom severity (Kay et al., 1987). We calculated chlorpromazine equivalent dosages (CPZ) at the scan date for all individuals with psychosis with complete medication information following previously established norms (Gardner et al., 2010).

Exclusion criteria for all individuals were an IQ less than 70 based on medical history/WASI-II (McCrimmon & Smith, 2013), contraindication to MRI scan, DSM-5 (*Diagnostic and statistical manual of mental disorders: DSM-5™*, 2013) diagnosis of substance-induced psychosis, or psychotic disorder due to medical condition based on SCID interview (First, 2015), and known organic brain damage.

2.1.2 | Data set #2: Chronic psychosis

Individuals with psychosis in this data set were also diagnosed utilizing the SCID-5-Research version criteria (First, 2015), and the duration of illness was determined via the SCID interview. The PANSS was administered to determine symptom severity (Kay et al., 1987), and we calculated CPZ (on the day of scanning) for all individuals with psychosis.

Exclusion criteria for all individuals included contraindication to an MRI scan or a history of brain disorder, neurological injury, or substance abuse. Additional exclusion criteria for HC were a history of psychiatric illness themselves or in first or second-degree relatives, assessed with the Mini-International Neuropsychiatric Interview (Sheehan et al., 1998).

2.2 | Image acquisition

2.2.1 | Data set #1: Early course psychosis

A 3 T MAGNETOM Prisma (Siemens Healthcare, Erlangen, Germany) with 32 channel head coils was used to scan the participants. A whole-brain, high-resolution three-dimensional T1-weighted magnetization prepared rapid gradient echo (MPRAGE) was used to acquire 240 sagittal slices with a field of view = $256 \times 240 \times 166$ mm^3, 0.8 mm isotropic voxels, TR = 2400 ms, TE = 2.22 ms, flip angle = 8°.

2.2.2 | Data set #2: Chronic psychosis

A 3 T MAGNETOM Prisma (Siemens Healthcare, Erlangen, Germany) with 64 channel head–neck coils was used to collect the structural MRI data. A whole brain, high-resolution three-dimensional T1-weighted magnetization prepared rapid gradient echo (MPRAGE) sequence was used to acquire 240 sagittal slices with a field of view = 224 × 224 mm^2, 1 mm^3 isotropic voxel, TR = 2300 ms, TE = 2.33 ms, flip angle = 8°.

2.3 | Preprocessing

Both data sets were processed employing the same processing pipeline (https://github.com/pnlbwh/pnlpipe). Structural T1 images underwent visual quality control, were realigned to the AC-PC line and were centered. Subsequently, brain masks were generated using 3D Slicer (software version 4.5; www.slicer.org) and edited manually. Images were then parcellated into 176 gray and white matter regions using FreeSurfer version 6® (Fischl, 2012). We derived intracranial volume, excluding the ventricle volume (ICV) and LV volumes, from this FreeSurfer segmentation for statistical analyses.

2.4 | Segmentation of the ChP

While FreeSurfer® is a widely accepted tool for segmentation and parcellation of gray matter, previous studies reported overestimating and misidentifying structures surrounded by high-intensity voxels (Cherbuin et al., 2009; Tae et al., 2008) (see Figure S1 demonstrating errors in FreeSurfer segmentation of ChP when compared with manual segmentation). We, therefore, opted to segment the ChP manually.

Based on the guidance of our neuroanatomy team (Drs. Jarrett Rushmore, Nikos Makris, and Edward Yeterian), we focused our segmentation on the trigonum ventriculi in the atrium of the lateral ventricle. The trigonum ventriculi is a triangular cavity of the lateral ventricles at the transition between the body of the lateral ventricles and the occipital and temporal horns, which contains the most reliably identifiable and sizable portion of the ChP, distinct from the surrounding structures (Figure 1). After identifying the trigonum ventriculi, we primarily utilized the coronal view to segment the ChP. Next, editing of the segmentation was conducted in axial and sagittal views, making sure not to include voxels from white or gray matter structures bordering the ventricle (e.g., the corpus callosum body superiorly, the fornix, hippocampus, thalamus, the splenium of the corpus callosum medially, the vertical portion of the caudate laterally, and the cerebral

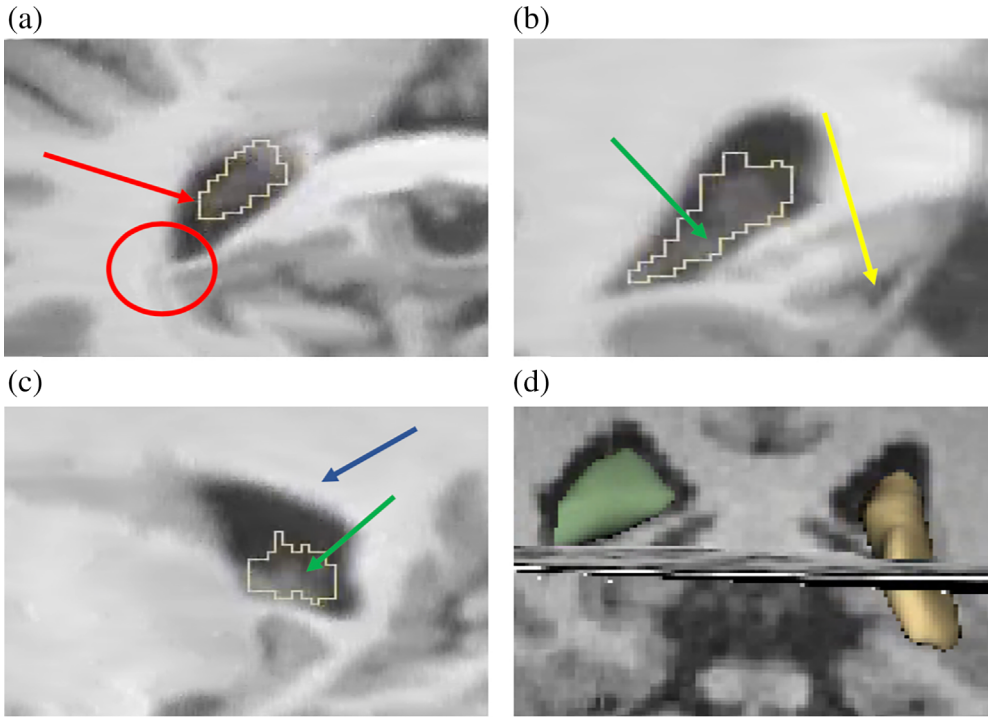

FIGURE 1 Manual segmentation of the Choroid Plexus using Slicer® (a) Axial view (b) Coronal view (c) Sagittal view. The coronal view was foremost used to guide the manual segmentation (b). ChP voxels were defined as hyperintense voxels within the ventricles. Voxels surrounded by clearly identified ChP tissue and located immediately next to a hypointense non-ChP voxel were included. In the case of two adjacent voxels with the same density at the boundary, the inner one was included (*red arrow*), and the outer one was excluded (*red circle*). After the segmentation in the coronal view, editing was conducted in the axial and sagittal view (a, c), making sure not to include grey or white matter, especially at the boundaries of the lateral ventricles (*green arrow*), thalamus (*yellow arrow*), and corpus callosum (*blue arrow*). Further, a *simultaneous 3D image* (d) served to check for holes, gaps, and islands of (non-) ChP tissue, which we then eliminated manually.

white matter inferiorly). Finally, the 3D view was used to complete the manual segmentation process (Figure 1). Last, we extracted the ChP volume measurements from the ChP segmentation for both hemispheres.

2.5 | Intra- and inter-rater reliability

OS and MS carried out all segmentations. To test intra-rater reliability, 10 randomized individuals were segmented twice by the same rater, revealing an intraclass correlation coefficient of .87, considered good to excellent reliability (Cicchetti & Nelson, 1994; Koo & Li, 2016). Ten randomized individuals were also manually segmented by both raters, revealing an intraclass correlation coefficient of .93. Given that the inter-rater reliability cannot be higher than the intra-rater reliability, we can assume an intraclass correlation coefficient of .87, which is considered good to excellent reliability (Cicchetti & Nelson, 1994; Koo & Li, 2016).

2.6 | Statistical analyses

We performed all statistical analyses using SPSS version 27 and GraphPad Prism 9. Normalized (by ICV, as derived from FreeSurfer) left and right ChP and LV volumes were utilized for all analyses. Again, we conducted the same statistical analyses for data sets #1 and #2 in parallel. We opted for this approach (instead of combining the data sets) because the two data sets were collected as part of two independent cohorts at two different sites.

2.6.1 | Group comparisons

ChP volume

To test for ChP enlargement, we calculated two ANCOVAs (for left and right hemispheres separately) with normalized ChP volume as the dependent variable, group (individuals with psychosis versus HC) as the independent variable, and sex and age as covariates. A p-value < .025 was considered significant (Bonferroni correction for two tests).

LV volume

Given the functional and structural connection between the ChP and LV, we decided to explore the role of LV volumes for our analyses. Therefore, we calculated two additional ANCOVAs to compare the normalized LV volumes between groups. Normalized LV volumes were included as the dependent variable, the group (individuals with psychosis versus HC) was the independent variable, and sex and age were covariates. A p-value < .025 was considered significant (Bonferroni correction for two tests).

Sensitivity analyses

As a sensitivity analysis, we repeated the group comparisons for data set # 1, only including individuals with schizophrenia ($n = 21$) and healthy individuals ($n = 30$).

2.6.2 | Correlation analyses in individuals with psychosis

ChP and LV volume

To further elucidate the relationship between ChP and LV volumes, we computed additional partial correlation analyses (corrected for sex and age). We calculated the association between normalized ChP volumes and normalized LV volumes separately for each hemisphere in individuals with psychosis. A p-value < .025 was considered significant (Bonferroni correction for two tests).

ChP and clinical variables

Last, we calculated partial correlations (corrected for age and sex) between normalized ChP volumes and symptom severity (defined by PANSS total, positive, and negative scores), CPZ, and duration of illness in individuals with psychosis. A p-value < .005 was considered significant (Bonferroni correction for 10 tests).

3 | RESULTS

3.1 | Demographics

Data set #1 comprised 41 individuals with psychosis and 30 HC. Data set #2 comprised 30 individuals with psychosis and 34 sex and age-matched HC. Because of age and sex differences in data sets #1 and 2 (see Table 1), we opted to include these variables as covariates in all analyses. For more demographical and clinical information, please see also Table 1.

3.2 | Data set #1: Early course psychosis

3.2.1 | Group comparisons

ChP volume

Individuals with early course psychosis presented with significantly higher left and right normalized ChP volumes than HC (left: $F [1, 67] = 22.23$, $p < .00010$, partial $\eta^2 = .25$; right: $F [1, 67] = 20.30$, $p < .00010$, partial $\eta^2 = .23$) (Table 2, Figure 2). The differences remained significant when controlling for normalized LV volumes as an additional covariate (left: $F [1, 66] = 26.57$, $p < .00010$, partial $\eta^2 = .29$; right: $F [1, 66] = 21.03$, $p < .00010$, partial $\eta^2 = .24$).

LV volume

Individuals with early course psychosis demonstrated increased left and right LV volumes, which reached the significance threshold only for the right LV (left: $F [1, 67] = 2.89$, $p = .094$, partial $\eta^2 = .041$, right: $F [1, 67] = 6.10$, $p = .016$, partial $\eta^2 = .083$) (Table 3).

Sensitivity analyses

We repeated the group comparisons, including individuals with schizophrenia ($n = 21$) and healthy individuals ($n = 30$). We again observed a difference in ChP volumes (left: $F [1, 47] = 14.89$, $p < .00010$, partial $\eta^2 = .24$; right: $F [1, 47] = 15.03$, $p < .00010$,

TABLE 1 Demographical variables.

	Healthy controls	Individuals with psychosis	Test statistic
Data set #1: Early course psychosis			
n (%)	30 (42.30%)	41 (57.70%)	
Age in years (mean ± SD)	25.03 ± 4.52	21.44 ± 4.01	t (69) = 3.54, $p < .0010$
Sex (*n*/%)	F: 12/40% M: 18/60%	F: 15/36.60% M: 26/63.40%	$\chi^2 = .086$, $p = .77$
Education in years (mean ± SD)	15.77 ± 2.09	13.09 ± 1.59	t (53) = 5.40, $p < .0010$
Duration of illness in years (mean ± SD)		1.78 ± 1.17	
PANSS total (mean ± SD)		47.38 ± 9.81	
PANSS negative symptoms (mean ± SD)		12.61 ± 4.79	
PANSS positive symptoms (mean ± SD)		13.27 ± 4.16	
Data set #2: Chronic psychosis			
n (%)	34 (53.13%)	30 (46.87%)	
Age in years (mean ± SD)	32.50 ± 9.10	33.07 ± 9.48	t (62) = −.24, $p = .81$
Sex (*n*/%)	F: 13/38.24% M: 21/61.76%	F: 11/36.67% M: 19/63.33%	$\chi^2 = .017$, $p = .90$
Education in years (mean ± SD)	14.91 ± 2.71	13.93 ± 2.95	t (62) = 1.38, $p = .17$
Duration of illness in years (mean ± SD)		7.96 ± 6.45	
PANSS total (mean ± SD)		57.13 ± 15.38	
PANSS negative symptoms (mean ± SD)		15.60 ± 6.31	
PANSS positive symptoms (mean ± SD)		11.80 ± 4.77	

Abbreviations: PANSS, positive and negative symptom scale; SD, standard deviation (Kay et al., 1987).

TABLE 2 Group comparison for ChP volumes.

	Healthy controls	Individuals with psychosis	Test statistic (ANCOVA, corrected for age and sex)	Test statistic (ANCOVA, corrected for age, sex, and normalized LV volume)
Data set #1: Early course psychosis				
Normalized ChP volume left hemisphere in mm^3 (mean ± SD)	.00092 ± .00019	.0012 ± .00020	F (1, 67) = 22.23, $p < .00010$*, $\eta^2 = .25$	F (1, 66) = 26.57, $p < .00010$*, $\eta^2 = .29$
Normalized ChP volume right hemisphere in mm^3 (mean ± SD)	.00087 ± .00016	.0011 ± .00019	F (1, 67) = 20.30, $p < .00010$*, $\eta^2 = .23$	F (1, 66) = 21.03, $p < .00010$*, $\eta^2 = .24$
Data set #2: Chronic psychosis				
Normalized ChP volume left hemisphere in mm^3 (mean ± SD)	.00069 ± .00043	.00089 ± .00040	F (1, 60) = 3.45, $p = .068$, $\eta^2 = .054$	F (1, 59) = .30, $p = .58$, $\eta^2 = .0050$
Normalized ChP volume right hemisphere in mm^3 (mean ± SD)	.00068 ± .00038	.00081 ± .00042	F (1, 60) = 1.72, $p = .20$, $\eta^2 = .028$	F (1, 59) = .005, $p = .94$, $\eta^2 < .00010$

Abbreviations: ChP = choroid plexus; SD, standard deviation.
*$p < .025$ (after Bonferroni correction for two tests).

partial $\eta^2 = .24$). Group differences for the LV were only significant for the right hemisphere (left: F [1, 47] = 2.82, $p = .10$, partial $\eta^2 = .057$, right: F [1, 47] = 6.35, $p = .015$, partial $\eta^2 = .12$).

3.2.2 | Correlation analyses in individuals with psychosis

ChP and LV volume

We did not observe a significant correlation between the left normalized ChP volume and the left normalized LV volume ($r = -.12$; $p = .46$). We also did not see a significant correlation between the right normalized ChP volume and right normalized LV volume ($r = .012$, $p = .94$) (Table S1).

ChP and clinical variables

Partial correlations (corrected for age and sex) did not show significant correlations between normalized ChP volumes and total, positive, or negative symptom severity or duration of illness. A positive correlation between CPZ and ChP volumes (left: $r = .43$, $p = .031$; right: $r = .36$, $p = .079$) did not reach the Bonferroni-corrected significance threshold (Table S2).

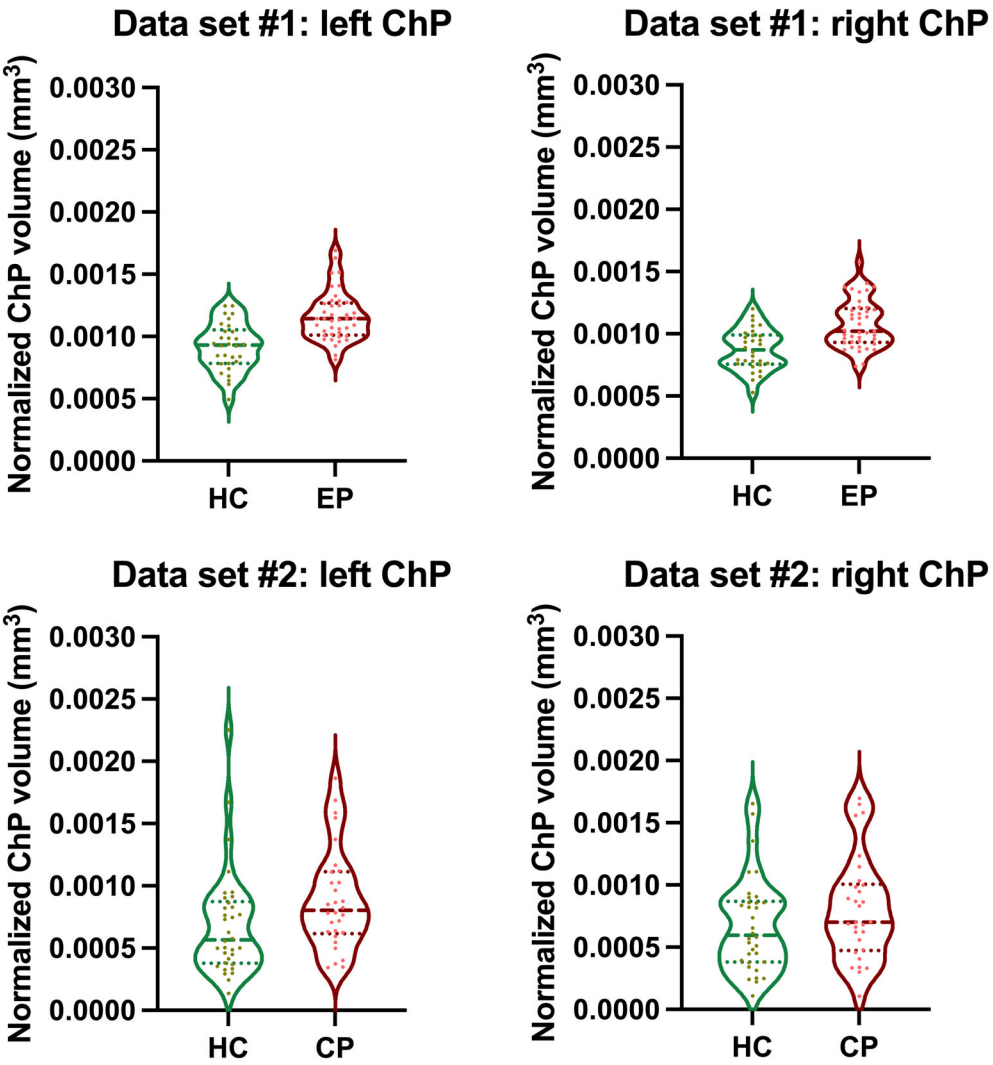

FIGURE 2 Choroid Plexus volume. Violin plots for Choroid Plexus (ChP) volume in (a) early course psychosis (ECP) individuals and healthy controls (HC) and (b) chronic psychosis (CP) individuals and (HC). Broken lines: median; Dotted lines: quartiles.

3.3 | Data set #2: Chronic psychosis

3.3.1 | Group comparisons

ChP volume

Individuals with chronic psychosis presented with higher left and right normalized ChP volumes, which did not reach the significance threshold (left: F [1, 60] = 3.45, $p = .068$, partial $\eta^2 = .054$; right: F [1, 60] = 1.72, $p = .20$, partial $\eta^2 = .028$) (Figure 2, Table 2). The differences were also not significant when controlling for normalized LV volume as an additional covariate (left: F [1, 59] = .30, $p = .58$, partial $\eta^2 = .0050$; right: F [1, 59] = .0050, $p = .94$, partial $\eta^2 < .00010$).

LV volume

Individuals with chronic psychosis exhibited higher normalized left and right LV volumes which did not reach the significance threshold (left: F [1, 60] = 5.12, $p = .027$, partial $\eta^2 = .079$; right: F [1, 60] = 3.85, $p = .054$, $\eta^2 = .060$) (Table 3).

3.3.2 | Correlation analyses in individuals with psychosis

ChP and LV volume

Partial correlations (corrected for age and sex) demonstrated that larger normalized ChP volumes were significantly associated with larger normalized LV volumes (left: $r = .54$, $p = .0030$; right: $r = .68$; $p < .0010$) in individuals with psychosis (Table S1).

ChP and clinical variables

Partial correlations (corrected for age and sex) showed no significant correlations between normalized left or right ChP volume and total, positive, and negative symptom severity, current CPZ, or duration of illness (Table S2).

4 | DISCUSSION

The present study is the first to investigate ChP volumes in individuals with psychosis utilizing a manual segmentation method. As

TABLE 3 Group comparison for LV volume.

	Healthy controls	Individuals with psychosis	Test statistic (ANCOVA, corrected for age and sex)
Data set #1: Early course psychosis			
Normalized LV volume left hemisphere in mm^3 (mean ± SD)	.0057 ± .0021	.0065 ± .0026	$F(1, 67) = 2.89$, $p = .094$, $\eta^2 = .041$
Normalized LV volume right hemisphere in mm^3 (mean ± SD)	.0048 ± .0017	.0061 ± .0022	$F(1, 67) = 6.10$, $p = .016^*$, $\eta^2 = .083$
Data set #2: Chronic psychosis			
Normalized LV volume left hemisphere in mm^3 (mean ± SD)	.0067 ± .0035	.0091 ± .0051	$F(1, 60) = 5.12$, $p = .027$, $\eta^2 = .079$
Normalized LV volume right hemisphere in mm^3 (mean ± SD)	.0063 ± .0028	.0083 ± .0051	$F(1, 60) = 3.85$, $p = .054$, $\eta^2 = .060$

Abbreviations: LV, lateral ventricle; SD, standard deviation.
*$p < .025$ (after Bonferroni correction for two tests).

hypothesized, we report higher ChP volumes in individuals with psychosis than in healthy individuals. Interestingly, group differences were significant when comparing early course psychosis and healthy individuals but did not reach the significance threshold when comparing individuals with chronic psychosis and healthy individuals. While these findings might suggest that ChP enlargements are more pronounced around disease onset, some caution is needed, since several other factors (e.g., diagnosis, medication, IQ, smoking, substance use), which were not fully explored here, can also have an impact on the results, they might also suggest that ChP enlargements are more pronounced around disease onset. Further, more extensive studies are needed to follow up on this finding and the association between the ChP and LV.

4.1 | ChP volume

Aligning with two other MRI studies of the ChP volume in psychosis (Lizano et al., 2019; Zhou et al., 2020), we observe higher left and right ChP volumes in individuals with psychosis. However, comparisons were statistically significant only for early course psychosis. First, we would like to acknowledge that our sample size is relatively small, and our results are, therefore, preliminary.

As highlighted above, two previous studies examined ChP volume in psychosis. The first included individuals with chronic psychosis, and the second focused on treatment-naïve first-episode psychosis. Contrary to our findings, the first reported significant ChP enlargements and an association between increased ChP volume and elevated peripheral pro-inflammatory IL-6 (Lizano et al., 2019). The second MRI study in psychosis demonstrated a correlation between ChP enlargement and "allostatic load," calculated based on cardiovascular, metabolic, neuroendocrine, and immune-inflammatory markers. The authors suggested that this correlation indicates that the ChP can be considered a structural biomarker for the interaction between the central nervous system and peripheral processes (e.g., inflammation) in the early stage of psychosis (Zhou et al., 2020). Here, we found ChP enlargements in psychosis in both data sets. However, they only reached the significant threshold for the early-course psychosis data set. While this finding might be related to the relatively small sample, we would also like to highlight that we used a more accurate manual segmentation method than previous studies.

Aligning with the idea that ChP enlargements might be related to neuroinflammation are post-mortem studies that revealed an increased pro-inflammatory gene expression in the ChP in individuals with psychosis (Kim et al., 2016). Supporting evidence comes from preclinical studies that characterize the ChP as a central mediator between peripheral and central inflammation (Goldim et al., 2019; Hubert, Dumot, et al., 2019; Mortazavi et al., 2014; Szmydynger-Chodobska et al., 2009). Moreover, imaging studies have described ChP enlargements related to several neuroinflammatory disorders, such as sepsis, multiple sclerosis, and lupus erythematosus (Dixon & Pérez, 2020; Engelhardt & Sorokin, 2009; Hubert, Chauveau, et al., 2019; Ricigliano et al., 2021; Rudin, 1981).

While studies examining the ChP in psychosis are still sparse, a plethora of evidence supports the role of inflammation in the pathophysiology of psychosis. Several studies report elevated levels of peripheral inflammatory markers in psychosis (Schlaaff et al., 2020), extensive blood–brain barrier leakage in a subset of individuals with psychosis (Kamintsky et al., 2020), and increased immune cell transmigration into the brain in those with psychosis (Cai et al., 2020). While positron emission tomography (PET) studies of activated glial cells in individuals with psychosis remain inconclusive (Marques et al., 2019; Plaven-Sigray et al., 2018), diffusion MRI studies have shown that individuals with psychosis present with increased free-water levels during the early stages of the disorders that might be associated with an acute immunological response of the brain (Lyall et al., 2018; Pasternak et al., 2012). Indeed, a large, multisite study in psychosis supports this claim by showing a correlation between increased extracellular free-water and peripheral pro-inflammatory markers (Di Biase et al., 2020).

In light of these previous findings, the interpretation that ChP volumes might reflect an inflammatory brain response in the early rather

than later stages of psychosis is compelling. However, as detailed in the introduction, the ChP plays a crucial role in maintaining brain homeostasis in general (Alshehri et al., 2015; Brown et al., 2004; Szmydynger-Chodobska et al., 2009; Turner et al., 2014) and constitutes a main interface between the periphery and central nervous system. In particular, the ChP forms the blood-CSF barrier and, together with the blood–brain barrier and the glymphatic system, controls the internal brain milieu's homeostasis, removes toxic waste, and provides the clean environment the brain requires to function optimally (Achariyar et al., 2016; Jessen et al., 2015; Johanson et al., 2011; Shetty & Zanirati, 2020). A failure of this clearance system has been associated with several neurological and psychiatric disorders (Reddy & van der Werf, 2020; Segawa et al., 2021; Yan et al., 2021). While studying the brain's clearance system in-vivo is challenging, previous studies have suggested that increased free-water in early course psychosis might be a proxy for the glymphatic system performance (Demiral et al., 2019). Thus, future multi-modal studies, including blood and CSF markers and different types of imaging (e.g., PET), are needed to parse the role of the ChP for inflammation and the clearance system in psychosis.

4.2 | Association between ChP volume and clinical variables

We did not observe significant correlations between ChP volumes and total symptom severity for individuals with chronic psychosis, although the left ChP volume had a positive correlation with total symptom severity close to the significance threshold. It is important to note that in both data sets, individuals with psychosis were relatively stable clinically, and this small range of PANSS scores might contribute to the limited findings relating ChP to clinical symptomatology. Therefore, while previous MRI studies also reported no correlation between ChP volume and symptom severity (Lizano et al., 2019), more extensive and better-powered studies are needed to fully understand the relationship between ChP volume increases and the pathophysiology of psychosis.

Medication dosage on the scan day was significantly higher in data set #2 compared with data set #1. This fact is of particular interest given previous evidence of the interaction between antipsychotic medication and inflammation in psychosis (Pandurangi & Buckley, 2020). However, we did not observe a significant relationship between medication dosage on the day of the scan and increased ChP volumes in either data set. Furthermore, preclinical studies demonstrated a relationship between the dopamine and serotonin system and the ChP blood flow, not the ChP volume. Nonetheless, future research is needed to characterize the relationship between the ChP volumes and brain levels of neurotransmitters to determine whether the ChP might be a target for antipsychotic drugs (Castellani et al., 2019; Nakayama et al., 2007). Additionally, future studies should examine the influence of lifetime antipsychotic medication, different types of antipsychotic medication, and other medications, such as lithium, which might have anti-inflammatory properties.

4.3 | Association between ChP volume and lateral ventricles

Our tests for enlarged LV reach significance levels only for the right LV in early psychosis, although increased LV volumes are widely recognized as a hallmark of psychosis (Alliey-Rodriguez et al., 2019; Del Re et al., 2016; Johnstone et al., 1976). We believe that our failure to replicate these findings (van Erp et al., 2016) is most likely related to our relatively small sample and the exploratory nature of our study.

Notably, we observe a positive correlation between ChP and LV volumes in chronic psychosis, suggesting that ChP enlargements might contribute to LV abnormalities. Indeed, previous studies demonstrate that ChP pathological growth could cause ventricular enlargement in normal pressure communicating hydrocephalus (Maurizi, 1987). Additionally, previous CT studies report correlations between ChP calcifications and LV enlargement in psychosis (Kay et al., 1991). These findings may suggest that LV enlargement is a long-term consequence of ChP-related pathology, and thus, the finding that this relationship is observed predominantly in chronic psychosis is not surprising. However, larger longitudinal studies are needed to understand the relationship between ChP, LV, and CSF in psychosis.

4.4 | Limitations and future directions

We acknowledge several limitations in the present study. As already highlighted, our sample size was relatively small, and our results are preliminary. Additionally, while we investigate the ChP in two distinct cohorts (one early course and one chronic) utilizing the same processing and analysis pipelines, longitudinal multi-modal studies are needed to characterize the role of the ChP over illness trajectory, and both cohorts in this study had baseline data only. In addition, we would like to acknowledge that the different imaging resolutions between data sets might influence our findings, where a higher resolution may provide a more accurate volumetric characterization of the ChP and LV volumes.

Furthermore, we believe that using manual parcellation is one of the strengths of our analysis, given its novelty and its excellent intra- and inter-rater reliability. However, future studies are needed to further validate the manual segmentation method. Also, since our method is very time-consuming, developing better-automated segmentation methods is critical when examining the ChP in large-scale studies. We believe that our manual segmentation method may be used to train automated machine learning-based approaches in the future.

Further, while we examined the association between ChP volume and symptom severity/medication/duration of illness and corrected our analyses for age and sex, we were not able to investigate the influence on ChP volume of other variables, such as markers of peripheral inflammation, more defined diagnosis and medication information, smoking, substance abuse, race, or cognitive functioning (Devorak et al., 2015; Lee et al., 2018; Lizano et al., 2019; Nixon, 2008; Rudin, 1980; Serot et al., 2003).

Of particular note, the ChP is involved in many processes. Generally, the ChP is responsible for CSF production and preserving brain homeostasis (Szmydynger-Chodobska et al., 2009). Furthermore, it may be part of the neurogenic system (Nogueira et al., 2014) and thus engaged in guarding the limbic system (Rudin, 1980) and modulating the neurogenesis in the hippocampus (Demeestere et al., 2015). Structural and functional abnormalities of the limbic system and the hippocampus are among the most consistent findings in individuals with psychosis (Baglivo et al., 2018; Del Arco & Mora, 2009; Francis et al., 2013; Haukvik et al., 2015; Haukvik et al., 2018; Suzuki et al., 2005; Wood et al., 2001; Zhong et al., 2016). Thus, future and more extensive studies are needed to characterize the relation between ChP abnormalities and the pathophysiology of psychosis.

Lastly, it is critical to note that the enlargement of the ChP may be associated with peripheral inflammation. Previous studies have demonstrated peripheral inflammation in individuals with psychosis (Potvin et al., 2008; Upthegrove et al., 2014), and one post-mortem study showed that the ChP responds to peripheral inflammatory signals by upregulating pro-inflammatory genes in psychosis (Kim et al., 2016). Furthermore, an increase in the ChP volume has been demonstrated in reaction to the complex regional pain syndrome- a disorder with peripheral and central components (Hubert, Chauveau, et al., 2019). Thus, more extensive longitudinal studies are required to characterize the ChP over the illness trajectory, its interaction with peripheral and central markers, and its relationship with the clinical presentation of the disorder.

5 | CONCLUSION

The present study is the first to utilize manual segmentation of the ChP to study its role in psychosis. In summary, we demonstrated significant ChP enlargement in individuals with early-course psychosis and a positive association between ChP and LV volumes in chronic psychosis. We speculate that ChP enlargement might reflect a neuroinflammatory response around disease onset. Thus, ChP volume may serve as a promising marker for monitoring response to novel diagnostic and therapeutic strategies. However, more extensive longitudinal studies that further examine the influence of, for example, medication, symptom severity, duration of illness, substance use, and peripheral inflammation are needed to follow up on our findings.

ACKNOWLEDGMENTS

The authors would like to thank all individuals for participating in this study. This work was supported by the National Institutes of Health (NIH) (grant numbers R01MH102377) (PI: Dr. Marek Kubicki), K24MH110807 (PI: Dr. Marek Kubicki), 5U01MH109977-04 (PIs: Drs. Martha E. Shenton and Alan Breier, as well as Drs. Daphne Holt, Kathryn E. Lewandowski, Matcheri S. Keshavan, and Dost Öngür). We acknowledge the core facility MAFIL supported by the Czech-BioImaging large RI project (LM2018129 funded by MEYS CR) to obtain scientific data presented in this article. We further acknowledge support by the Harvard Medical School Livingston Fellowship Award (PI: Dr. Johanna Seitz-Holland), the Young Investigator Grant sponsored by Mary and John Osterhaus and the Brain & Behavior Research Foundation (PI: Dr. Johanna Seitz-Holland), and the Evangelische Studienstiftung Villigst (PI: Carina Heller).

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data are currently not available but part of the data will be available publicly (Human Connectome Project).

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How to cite this article: Senay, O., Seethaler, M., Makris, N., Yeterian, E., Rushmore, J., Cho, K. I. K., Rizzoni, E., Heller, C., Pasternak, O., Szczepankiewicz, F., Westin, C.-F., Losak, J., Ustohal, L., Tomandl, J., Vojtisek, L., Kudlicka, P., Kikinis, Z., Holt, D., Lewandowski, K. E., … Kubicki, M. (2023). A preliminary choroid plexus volumetric study in individuals with psychosis. *Human Brain Mapping*, *44*(6), 2465–2478. https://doi.org/10.1002/hbm.26224