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Difficulties during delivery, brain ventricle enlargement and cognitive impairment in first episode psychosis

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Original Article

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Abstract

Background. Patients with a first episode of psychosis (FEP) display clinical, cognitive, and structural brain abnormalities at illness onset. Ventricular enlargement has been identified in schizophrenia since the initial development of neuroimaging techniques. Obstetric abnormalities have been associated with an increased risk of developing psychosis but also with cognitive impairment and brain structure abnormalities. Difficulties during delivery are associated with a higher risk of birth asphyxia leading to brain structural abnormalities, such as ventriculomegaly, which has been related to cognitive disturbances.

Methods. We examined differences in ventricular size between 142 FEP patients and 123 healthy control participants using magnetic resonance imaging. Obstetric complications were evaluated using the Lewis–Murray scale. We examined the impact of obstetric difficulties during delivery on ventricle size as well as the possible relationship between ventricle size and cognitive impairment in both groups.

Results. FEP patients displayed significantly larger third ventricle size compared with healthy controls. Third ventricle enlargement was associated with diagnosis (higher volume in patients), with difficulties during delivery (higher volume in subjects with difficulties), and was highest in patients with difficulties during delivery. Verbal memory was significantly associated with third ventricle to brain ratio.

Conclusions. Our results suggest that difficulties during delivery might be significant contributors to the ventricular enlargement historically described in schizophrenia. Thus, obstetric complications may contribute to the development of psychosis through changes in brain architecture.

Introduction

Schizophrenia is a complex disorder characterized by psychotic symptoms and associated with increased medical co-morbidity and reduced life expectancy (Kirkpatrick et al., 2013). Schizophrenia is considered to result from a gene–environment interaction with several contributing risk factors, including obstetric complications (OCs) (Cannon, Jones, & Murray, 2002; Davies et al., 2020). In terms of patients' outcomes, recent research highlights the influence of pre and perinatal insults on measures of cognition (Amoretti et al., 2022), psychopathology (Peralta et al., 2011; Verdolini et al., 2023), and brain structure (Costas-Carrera, Garcia-Rizo, Bitanihirwe, & Penadés, 2020), but also metabolic parameters (Garcia-Rizo et al., 2022, 2020; Garriga et al., 2019).

Ventricular enlargement has been widely described in patients with schizophrenia, initially, almost a century ago, using pneumoencephalographic imaging (Jacobi & Winkler, 1927) and then, in the seminal study by Johnstone et al. through computerized axial tomography (Johnstone, Frith, Crow, Husband, & Kreel, 1976). Subsequent meta-analyses confirmed the finding (Kuo & Pogue-Geile, 2019; Van Horn & McManus, 1992; Wright et al., 2000), describing enlargements in lateral ventricles and the third ventricle with medium-to-large effect sizes. Meta-analyses reported ventricular enlargements with moderate effect sizes in chronic patients but also in antipsychotic naïve first episode psychosis (FEP) patients, suggesting that the enlargement precedes psychotropic medication use (Haijma et al., 2013) and is related to developmental abnormalities, signaling a neurodevelopmental disturbance. Similar findings in lateral ventricles have also been reported in individuals with a high risk for psychosis (Sasabayashi et al., 2020) but

not observed in first-degree relatives (Cuesta et al., 2017) or in affective psychosis (Nakamura et al., 2007).

The ventricle-to-brain ratio (VBR) is a brain volumetric measurement calculated as a ratio of ventricular volume (i.e. lateral, III, and IV ventricles) to brain parenchymal volume (total white and gray matter) (Tate, 2018). The VBR is able to capture global atrophic changes in aging, disease, and/or injury and provides a measure of atrophy that is directly comparable to that of other subjects. A higher VBR is associated with volume decrease in different brain areas such as the thalamus, striatum, and temporal lobe in patients diagnosed with schizophrenia (Gaser, Nenadic, Buchsbaum, Hazlett, & Buchsbaum, 2004). These areas are involved in multiple cognitive domains, such as attention, executive function, and verbal memory.

In schizophrenia, ventriculomegaly is associated with negative symptoms and cognitive deficits (Konishi et al., 2018), with more significant enlargement reported for patients with global cognitive impairment compared to those whose cognition is preserved (Yasuda et al., 2020). In FEP patients lateral and third ventricle volumes were associated with the severity of negative symptoms (Cuesta et al., 2017).

The volume of the third ventricle, in particular, is the most frequently associated with deficits in neuropsychological performance, suggesting the involvement of periventricular diencephalic structures (Bornstein, Schwarzkopf, Olson, & Nasrallah, 1992). Cognitive impairment is a core feature of schizophrenia with attention, working memory, executive function, and verbal memory as the most affected domains (Valli, Tognin, Fusar-Poli, & Mechelli, 2012). These deficits can also be observed before illness onset and are associated with measures of outcome (Bowie & Harvey, 2006; Valli et al., 2012). In FEP patients cognitive impairment is related to negative symptoms and greater total PANNS score at follow-up (Mezquida et al., 2023).

OCs increase the risk of developing psychotic disorders, particularly schizophrenia (Cannon et al., 2002; Davies et al., 2020), and have been associated with an earlier age of onset (Baeza et al., 2021) and more severe psychopathology (Peralta et al., 2022). However, OCs are heterogeneous phenomena and recent research highlights the importance to differentiate between events occurring during gestation and during delivery (Mezquida et al., 2018). In individuals with psychosis, exposure to difficulties during delivery is associated with several outcome measures in terms of psychopathology (Mezquida et al., 2021), cognition (Sagué-Vilavella et al., 2022), and brain structure (Smith et al., 2015; Wortinger et al., 2020).

Delivery problems include multiple conditions such as premature rupture of membranes, umbilical cord prolapse, complicated cesarean delivery, and abnormal fetal presentation or use of forceps (Dars, Malik, Samreen, & Kazi, 2014; Ecevit et al., 2014; Leung & Lao, 2013; Mukhopadhyay & Arulkumaran, 2002).

Among delivery problems, hypoxia (OR 1.63), rupture of membranes (OR 1.86), and particularly premature rupture of membranes (OR 2.29) are significant risk factors for psychotic disorders (Davies et al., 2020). The common mechanism associated with increased schizophrenia risk is considered to involve fetal hypoxia (Cannon et al., 2002), a finding particularly robust for early-onset schizophrenia (Rosso et al., 2000). During delivery, the infant's brain is susceptible to different regional patterns of injury depending on the severity and duration of hypoxia and on gestational age but mostly affecting brain areas such as the parasagittal cortex, hippocampus, thalamus, and basal ganglia (De Haan et al., 2006; Herrera-Marschitz et al., 2014; Mercogliano & Poddar, 2021). The white matter dorsal and lateral to the external angles of the lateral ventricles is also sensitive to hypoxia, which can result in periventricular leukomalacia and over time may lead to ventriculomegaly (Collins & Popek, 2018). The effect of asphyxia on white matter has been reported to be greater in patients with schizophrenia than in healthy controls (Wortinger et al., 2021), suggesting an interaction between genetic predisposition and perinatal environmental exposures in the development of schizophrenia (Ursini et al., 2018). However, the latter is still debated (Vassos et al., 2022) and other studies did not observe a significant difference in the effect of asphyxia on the brain between patients and controls (Wortinger et al., 2020).

In schizophrenia, perinatal complications have been associated with impairments across most cognitive domains. However, in a recent meta-analysis, patients with schizophrenia exposed to OC showed poorer performance specifically in terms of verbal memory and working memory compared to patients with no OC history (Amoretti et al., 2022).

We, therefore, sought to examine the impact of difficulties during delivery on these two cognitive domains and on ventricular volumes. We focused on patients with FEP rather than established schizophrenia in order to minimize the potential impact of important confounders such as protracted illness and medication exposure.

We hypothesized that difficulties during delivery would be associated with increased ventricular size, especially in the FEP group compared to HC participants, with an interaction between group and exposure. We also hypothesized that such enlargement would be related to worse cognitive functioning in the two aforementioned cognitive domains, working memory, and verbal memory.

Material and methods

This study is a part of a multicenter study, (the PEPs study 'phenotype–genotype and environmental interaction. Application of a predictive model in first psychotic episodes'), which is a longitudinal cohort study examining gene × environment interactions on the pathway to psychosis.

Participants

The sample of the PEPs study included 335 FEP patients and 253 HC, recruited between January 2009 and December 2011. The inclusion criteria and characteristics of the study have been previously described in detail (Salagre et al., 2019). Briefly, subjects with FEP aged 7–35 years, presenting psychotic symptoms for less than 12 months, were recruited from the inpatient and outpatient units of 16 participating Spanish centers, members of the Center of Biomedical Research Network on Mental Health (CIBERSAM). Healthy controls were recruited at each site through advertisements and matched with patients by age (±10%), sex and parental socio-economic status (SES), measured with the Hollingshead-Redlich scale (±1 level). For the neuroimaging component of the study, a maximum time of 6 months was established from inclusion to scan time. All centers received the approval of their respective Independent Ethics Committee. Written informed consent was obtained from all participants prior to their participation in the study, and from parents/legal guardians for children under 16 years of age (children gave assent). In the present study, from the total sample, we included 142 FEP and 123 HC for whom both magnetic resonance imaging and data regarding obstetric complications exposure were available.

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History of obstetric complications (OCs) assessment

OCs were assessed using the Lewis–Murray scale through a maternal interview (Lewis, Owen, & Murray, 1989). The scale groups OCs in three categories, A, B, and C (Cannon et al., 2002; Mezquida et al., 2018) according to the type of complication defined as follows:

A. Complications of pregnancy (syphilis or rubella, rhesus isoimmunization/Rh incompatibility, severe preeclampsia, requiring hospitalization or induction of labor, and bleeding before delivery or threatened abortion).
B. Abnormal fetal growth and development (twin delivery, preterm birth before 37 weeks, or long-term after 42 weeks, weight at birth less than 2500 g, and any important physical abnormality).
C. Difficulties in delivery (premature rupture of membranes, duration of delivery more than 36 h or less than 3 h, umbilical cord prolapse, complicated cesarean delivery, abnormal fetal presentation, use of forceps, and being in an incubator for more than 4 weeks).

As our aim was to evaluate difficulties during delivery, patients were stratified as having or not having any event described in group C.

Image acquisition and processing

The MRI acquisition protocol for each scanner is described in online Supplementary Material. The FreeSurfer analysis package (v5.3, https://surfer.nmr.mgh.harvard.edu/) was used to generate measurements of cortical thickness and both cortical and subcortical volumes including ventricular volumes. The standard FreeSurfer processing pipeline was employed, which follows the workflow: motion and bias field correction, skull extraction, affine, and nonlinear alignment to the Talairach atlas, subcortical division, and cortical segmentation using the Desikan–Killiany atlas. For quality assurance, a visual inspection of the segmentation was performed by a neuroimaging technician, following the quality control protocol 2.0 of the ENIGMA consortium (https://enigma.ini.usc.edu/protocols/imaging-protocols).

Acquisition parameter characteristics are described in online Supplementary material.

In this multicenter study, data were collected from six distinct neuroimaging centers and different scanners (Siemens Magnetom Trio Tim 3T, Siemens Symphony 1.5T, Philips Achieva 3T, Philips Intera 1.5T, GE Signa Horizon MX 1.5T, and GE Signa Excite 1.5T). To adjust for site, we therefore employed the ComBat batch harmonization method.

Neuropsychological assessment

Neuropsychological performance was assessed using a battery of standardized neuropsychological tests, which includes the main cognitive domains proposed by the MATRICS initiative (Nuechterlein et al., 2008). This battery was composed by: Continuous Performance Test-II (CPT-II) (Homack & Riccio, 2006) to test Attention/Vigilance; Trail Making Test-A (Reitan & Wolfson, 1995) and Stroop test to test Processing Speed (Golden, 1978); Wisconsin Card Sorting Test (WCST) (Heaton, 1993) and TMT-B (Reitan & Wolfson, 2001) to test Executive Function; Digit span test of WAIS-III and Letter-number sequencing WAIS-III (Weschler, 1997) to test Working Memory; Controlled Oral Word Association Test (COWAT) (Ruff, Light, Parker, & Levin, 1996) and Animal words from Test Barcelona (Benito-Cuadrado, Esteba-Castillo, Böhm, Cejudo-Bolívar, & Peña-Casanova, 2002) to test Verbal Fluency; and finally, Verbal Learning test España-Complutense (TAVEC) (Benedet & Alexandre, 1998) to test Verbal Memory. Additionally, the Vocabulary subtest of WAIS-III was used to estimate premorbid IQ. Higher *T*-scores correspond to better performance in all cognitive domains. Details on the neuropsychological assessment, tests, and measures included for each cognitive domain are described in Sánchez-Torres (Sánchez-Torres et al., 2022).

Statistical analysis

Descriptive statistics were calculated for each sociodemographic, neuropsychological, and clinical variables. Continuous variables are presented as mean value ± standard deviation and compared using Student's *t* tests. Categorical variables were expressed as total number (percentages) and compared between groups using χ^2 tests. Difficulties in delivery were considered as a dichotomous variable (yes/no).

Generalized linear model (GLM) analyses were performed to examine the relationship between each independent variable and ventricle structure (third ventricle, fourth ventricle, left-lateral ventricle, right-lateral ventricle, and lateral ventricles). Independent variables were sex, age, chlorpromazine equivalent dose, diagnostic group (FEP/HC), difficulties during delivery (presence/absence), and finally the interaction of diagnosis and difficulties during delivery. Dependent variables were volume of the third ventricle of the fourth ventricle; volume of left lateral ventricle of the right lateral ventricle, and total volume of both lateral ventricles combined. We also adjusted by estimated total intracranial volume (ICV). Post-hoc comparisons to evaluate the interaction of diagnosis with difficulties during delivery on different ventricular structures were performed with Bonferroni correction of multiple comparisons (Table 2). We described the main effects (χ^2 wald; *p* value) for each of the main variables examined (diagnosis, difficulties during delivery, and interaction between diagnosis, and difficulties during delivery) for each ventricle (Table 2). To test the possible correlation between ventricle size and antipsychotic dose, we performed a correlation analysis between these variables.

For cognitive measures, a GLM analysis was performed to evaluate the effect of OC and third ventricle to brain ratio (3VTBR) on the two specific cognitive domains (working and verbal memory) that were associated with OCs in our previous meta-analysis. Independent variables included in the model were sex, age, chlorpromazine equivalent dose, diagnostic group (FEP/HC), presence or absence of difficulties during delivery, 3VTBR, and educational level. We also performed two other separate analyses for each cognitive domain, in which the interaction between 3VTBR and diagnosis, and the interaction between VTBR and difficulties during delivery were considered. Estimation parameters description for each main variable (diagnosis, difficulties during delivery and 3VTBR) in the analysis of both cognitive domains are reported in Table 3.

Statistical analyses were performed with statistical package for the social sciences (SPSS) (Version 22).

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Results

Sociodemographic, cognitive, and volumetric characteristics

Sociodemographic characteristics of the sample are described in Table 1. There were no significant between group differences in sex, age, or ethnicity. However, as expected, the groups significantly differed in terms of educational level (χ^2 36.88, $p < 0.001$), employment (χ^2 52.44, $p < 0.001$), and socioeconomic status (χ^2 16.52, $p = 0.005$), with higher levels in HC than patients.

The mean age for the FEP patients was 24 years, the mean duration of total episodes was 8.8 months, and the mean duration of untreated psychosis was 103.63 days, while the daily equivalent doses of Chlorpromazine in FEP patients were 561.50. Finally, approximately 14.3% of the sample had history of difficulties during delivery, with no significant difference between patients with FEP and HC.

Difficulties during delivery and the relation with ventricle enlargement in FEP and HC

Patients displayed a significantly larger third ventricle ($t = 2.72$, $p = 0.007$) compared with HC. The fourth, right, left, and total lateral ventricles were larger in the patients but the between group difference did not reach statistical significance, although

Table 1. Sociodemographic, cognitive, and volumetric characteristics of the sample

	FEP ($n = 142$)	Healthy controls ($N = 123$)	χ^2	p
Categorial variables				
Sex (female, *n*, %)	48 (34%)	46 (37%)	0.372	0.542
Ethnicity			6.789	0.341
Caucasian	125 (88%)	111 (90%)		
Educational level			36.883	<0.001
Basic education	33 (23%)	10 (8%)		
Secondary education	85 (51%)	55 (45%)		
Graduate/postgraduate education	23 (16%)	58 (47%)		
Working status			52.439	<0.001
Employed	29(21%)	54 (44%)		
Unemployed	42 (31%)	7 (6%)		
Student	68 (48%)	62 (50%)		
Socioeconomic status			16.524	0.005
High	22 (16%)	24 (20%)		
Medium/high	19 (13%)	23(19%)		
Medium	34 (24%)	45(37%)		
Medium/low	43 (30%)	25(20%)		
Low	22 (16%)	5 (4%)		
Lewis–Murray C (difficulties during delivery)			1.64	0.222
Yes	24 (17%)	14 (11%)		
No	118 (83%)	109 (89%)		
Continuum variables	(mean ± S.D.)	(mean ± S.D.)	*t*	*p*
Age (years)	23.5 ± 6.0 [12.0–35.5]	24.07 ± 6.0 [9.9–36.0]	−1.31	0.189
CPZ	561.5 ± 432.0	NA	NA	NA
Verbal memory	200.45 ± 73.73	281.97 ± 49.56	−14.93	<0.001
Working memory	71.78 ± 15.04	87.47 ± 26.63	−8.54	<0.001
3VTBR	0.0009 ± 0.00019	0.0008 ± 0.00019	3.84	<0.001
Third ventricle (mm^3)	1020.04 ± 285.03	931.46 ± 229.9	2.72	0.007
Fourth ventricle (mm^3)	1890.74 ± 520.51	1802.08 ± 503.53	1.40	0.162
Left lateral ventricle (mm^3)	7974.05 ± 3749.17	7172.00 ± 3480.72	1.79	0.075
Right lateral ventricle (mm^3)	7313.55 ± 3208.77	6701.35 ± 3287.09	1.53	0.127
Lateral ventricle (mm^3)	15287.59 ± 6611.24	13 778.68 ± 6540.09	1.85	0.065
Estimated intracranial volume (mm^3)	15 888 863.64 ± 169 719.73	1 614 924.87 ± 153 892.18	−1.30	0.194

CPZ, daily equivalent doses of chlorpromazine; NA, not applicable.

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Table 2. Main effects of, diagnosis group, Lewis C (difficulties during delivery) and its interaction (estimated marginal means and post-hoc comparisons with Bonferroni) on ventricles' volume (mm^3 /1000)

	Lewis C		Diagnosis				Diagnosis × Lewis C					
									Bonferroni post-hoc comparisons			
	Effect		Effect				Effect		*Psychosis*		*Control*	
	χ^2 Wald	*p* Value	χ^2 Wald	*p* Value	Psychosis adjusted mean (95% CI)	Controls adjusted mean (95% CI)	χ^2 Wald	*p Value*	*Lewis C + adjusted mean (95% CI)*	*Lewis C – adjusted mean (95% CI)*	*Lewis C + adjusted mean (95% CI)*	*Lewis C – adjusted mean (95% CI)*
Third ventricle	12.11	0.001	4.72	0.030	1072.20 1017–1127	971.02 905–1036	0.08	0.774	*1146.39* *1053–1238*	*998.00* *951–1044* *p = 0.015*	*1033.92* *918–1149* *P = 0.878*	*908.12* *859–956* *p < 0.001*
Fourth ventricle	0.13	0.716	3.51	0.061	1916.00 1795–2036	1725.89 1583–1868	0.047	0.828	*1922.36* *1720–2123*	*1909.72* *1808–2011* *p = 1.000*	*1750.81* *1498–2003* *p = 1.000*	*1700.98* *1594–1807* *p = 0.401*
Left-lateral-ventricle	0.19	0.656	4.11	0.042	8385.13 7539–9231	6933.42 5927–7939	1.07	0.299	8833.56 7413–10 253	7936.70 7222–8650 *p = 1.000*	6754.72 4975–8534 *p = .483*	7112.12 6357–7867 *p = .267*
Right-lateral-ventricle	0.09	0.762	4.49	0.034	7687.32 6936–8438	6343.48 5453–7232	1.32	0.249	8076.25 6817–9335	7298.39 6664–7932 *p = 1.000*	6116.72 4540–7693 *p = 0.378*	6570.24 5907–7233 *p = 0.282*
Lateral-ventricle	0.17	0.674	4.75	0.029	16 049.16 14 515–17 582	13 221.12 11 397–15 045	1.18	0.277	16 874.53 14 299–19 449	15 223.79 13 929–16 517 *p = 1.000*	12 857.52 9631–16 083 *p = 0.375*	13 584.72 12 215–14 953 *p = 0.205*

Lewis C, difficulties in delivery present or absent (±); CPZ, daily equivalent doses of chlorpromazine; CI, confidence interval.
Adjusted by age, sex, and total intracranial volume.
Data harmonized with COMBAT (center of acquisition).
* $p < 0.05$.

left lateral ventricle ($t = 1.79$, $p = 0.075$) and total lateral ventricle ($t = 1.85$, $p = 0.065$) showed a trend towards significance (Table 1).

To test the association between difficulties during delivery and ventricle volumes a GLM analysis was performed. In this analysis, the enlargement of the third ventricle was significantly associated with difficulties during delivery (χ^2 *wald* = 12.11, $p < 0.001$) and with diagnosis (χ^2 *wald* = 4.72, $p = 0.030$) but we observed no significant interaction between these two factors (χ^2 *wald* = 0.08, $p = 0.774$). Since both independent factors were associated with third ventricle enlargement, participants with both FEP and exposure to difficulties during delivery displayed the highest volumes (1146.4 mm^3/1000) followed by HC with difficulties during delivery (1033.9 mm^3/1000), then FEP patients without difficulties during delivery (998.0 mm^3/1000) and finally HC without difficulties during delivery (908.1 mm^3/1000) (Table 2 and Fig. 1).

We also performed a correlation analysis between third ventricle volume and chlorpromazine equivalent doses and observed no significant correlation (Pearson $r = -0.056$ $p = 0.516$, Spearman $r = -0.037$ $p = 0.671$).

Relation between difficulties during delivery and cognition

As expected, FEP patients performed significantly worse than HC across all cognitive domains (Table 1).

third ventricle to brain ratio (3VTBR) was inversely correlated with verbal memory performance ($p = 0.034$), thus worse performance was associated with greater ventricle enlargement (Fig. 2 and Table 3). We also examined the potential interaction between 3VTBR and difficulties during delivery on verbal memory performance and observed no significant effect (beta: −31 087.2; standard error: 52 518.7; $p = 0.554$). In a separate analysis, we examined whether there was an interaction between 3VTBR and diagnostic group on verbal memory, and observed no significant effect (beta: −65 228.3; standard error: 51 117.8; $p = 0.202$).

We observed no significant associations between 3VTBR and working memory.

Discussion

Our findings confirm an increased ventricular volume in patients with a FEP compared with HC in each part of the ventricular system examined, with significant differences in the third ventricle and trend level differences in the left lateral ventricle and total lateral ventricles.

Within the subsample of participants who had been exposed to difficulties during delivery, patients did not show a significantly increased volume of the third ventricle compared to HC. However, contrary to our hypothesis, there was no significant interaction between diagnosis and difficulties during delivery on ventricular enlargement, despite subjects with FEP and difficulties during delivery showing the largest volume of all subgroups. We also observed a significant association between larger 3VTBR and worse verbal memory performance in both patients and HC. However, there was no significant interaction between either 3VTBR and diagnosis or 3VTBR and difficulties during delivery on verbal memory.

The difference we observed in ventricle volume between HC and FEP patients is consistent with previous findings, with third ventricle enlargement reported in almost 2/3 of patients diagnosed with schizophrenia (McCarley et al., 1999) and third/lateral ventricle enlargement also observed in FEP (Fannon et al., 2000; Sasabayashi et al., 2020). Our results are thus in keeping with the suggestion that ventricular enlargement is not an epiphenomenon of chronic illness or prolonged medication exposure but might be neurodevelopmental in origin since it has been described in the earliest stages of the disease, especially in males (Nakamura et al., 2004). This enlargement might be related to abnormalities in the choroid plexus and its physiological

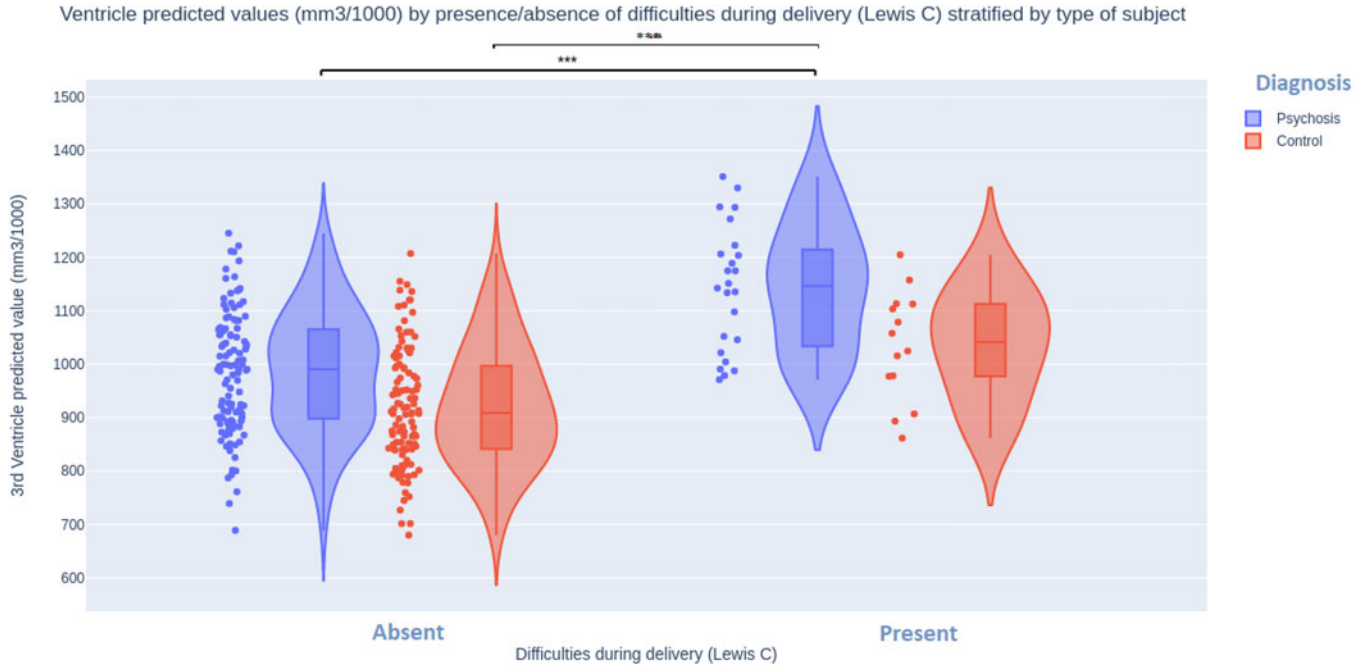

Figure 1. Generalized linear model third ventricle predicted values (mm^3/1000) by presence/absence of difficulties during delivery (Lewis C; present/absent) stratified by diagnosis (psychosis/control). Predicted third ventricle values are adjusted by covariates, age, sex, difficulties during delivery, diagnosis, chlorpromazine equivalent mean dose, and estimated total intracranial volume.

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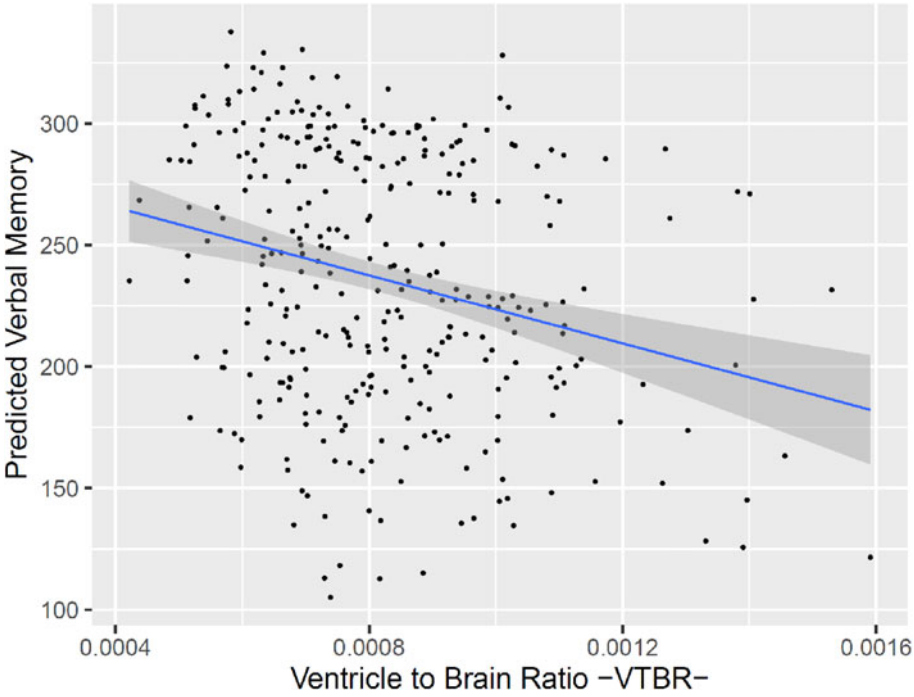

Figure 2. Generalized linear model predicted verbal memory values and third ventricle-to-brain ratio (FEP patients and controls). Predicted verbal memory values are adjusted by covariates, age, sex, difficulties during delivery, diagnosis, chlorpromazine equivalent mean dose, and educational level.

Table 3. Parameter estimation for cognitive outcomes (verbal memory and working memory)

	Working memory			Verbal memory		
	Beta	s.e.	*p*	Beta	s.e.	*p*
Diagnosis	−7.48	2.4	0.002	−48.26	10.0	<0.001
Difficulties during delivery	−0.76	2.5	0.763	−12.12	10.4	0.244
3VTBR	−7455.54	6516.7	0.253	−56 532.98	26 648.1	0.034

s.e., standard error; 3VTBR, third ventricle to brain ratio.
This analysis was controlled by age, sex, educational level, and chlorpromazine equivalents.

functions that have been observed in patients with schizophrenia (Haukvik et al., 2010a; Lizano et al., 2019). Increased choroid plexus volume in psychosis was observed to be correlated with worse cognitive function, regional brain atrophy, and increased ventricular size (Lizano et al., 2019).

Within delivery complications, perinatal asphyxia is considered the mechanism involved in brain changes such as smaller intracranial volume, total brain volume, white and gray matter volumes, and reduced total surface area, not only in patients with schizophrenia or bipolar disorder but also in HC (Wortinger et al., 2020). So, even though we employed perinatal adversity as a proxy measure for hypoxia during birth, our results on third ventricle volume are consistent with those of Wortinger et al., who observed no interaction between asphyxia and diagnosis in most areas of the brain (Wortinger et al., 2020). Similarly, Haukvik et al. reported an effect of obstetric complications on the volume of the nucleus accumbens (Haukvik et al., 2010a), the hippocampus (Haukvik et al., 2010b), and the cortical folding in Broca's area in both patients and controls (Haukvik et al., 2012).

Thus, our finding of a relationship between difficulties during delivery and third ventricle volume that was not significantly more pronounced in patients with psychosis, suggests that perinatal OCs may increase the risk of third ventricle enlargement with an additive effect (Wortinger et al., 2020). Falkai et al. hypothesized that OCs may exert a diffuse add-on effect leading to structural changes related to the pathophysiology of schizophrenia (Falkai et al., 2003). This summative effect has been suggested to act both by impacting brain development (Smeland et al., 2018) and impairing the resilience of the fetal brain (Murray, Bhavsar, Tripoli, & Howes, 2017). Furthermore, the relationship between genetic vulnerability for schizophrenia and perinatal adversity is still under debate (Ursini et al., 2018; Vassos et al., 2022), and a recent study in FEP showed no significant interaction between genetic risk of psychosis and obstetric vulnerability (Valli et al., 2023).

The enlargement in ventricular size has been reported to predict a longer time to remission of psychotic symptoms and poorer outcomes (Dazzan et al., 2015). It could thus be hypothesized that difficulties during delivery could be a risk factor for a worse prognosis considering that, also in our FEP sample, difficulties during delivery were associated with a more severe psychopathological profile (Peralta et al., 2022).

Our work also sought to examine the relationship between ventricular enlargement and cognition as well as its relationship with difficulties during delivery. In healthy subjects, third ventricle and total ventricular volume were reported to be associated

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with global cognition but also with specific cognitive domains, such as verbal memory and executive function (de Mélo Silva Júnior, Diniz, de Souza Vilanova, Basto, & Valença, 2022). In schizophrenia, among ventricular measures, third ventricular enlargement was the most frequently associated with cognitive performance, especially with dysfunctional frontal and limbic processing as well as with negative symptoms (Cuesta et al., 2017; McCarley et al., 1999). We observed that 3VTBR was associated with verbal memory. However, this finding was not specific to patients with FEP, as we also observed this relationship in HC. Furthermore, the interaction between 3VTBR and difficulties during delivery did not predict performance in either of the cognitive domains that we examined. The only meta-analysis to date that examined the relationship between cognitive dysfunction and OCs in schizophrenia reported an association between verbal memory deficits and OCs, but not specifically for difficulties during delivery (Mezquida et al., 2021). Yet a number of other environmental and genetic risk factors are considered to be involved in the pathophysiology of cognitive impairment in schizophrenia, such as family history of psychosis (Bora & Murray, 2014), childhood adversity (Wells et al., 2020), and substance abuse (Manning et al., 2009).

Several methodological limitations should be acknowledged in our study. Data on obstetric complications were gathered via a maternal interview, which could be associated with risk of recall bias in mothers of patients compared to mothers of HC. However, a study examining the validity of a retrospective OCs interview, Janssen-Cilag reported high concordance between medical records and maternal recall in schizophrenia research (Borrajo et al., 2011). The Lewis–Murray scale, though, records only a limited number of adverse events during gestation and delivery, while several others may have not been assessed. In addition, we employed difficulties during delivery as a proxy measure for perinatal hypoxia, yet the Lewi-–Murray scale does not include a rating of severity, therefore difficulties during delivery might be especially heterogeneous in terms of potential hypoxic consequences to the brain. The presence of difficulties during delivery does not exclude the presence of other difficulties during the gestational period, such as placental abnormalities, which might have confounded our results. The low number of participants with abnormalities during delivery might have also impacted the power of our analyses, increasing the odds of negative findings in terms of other ventricular areas and cognitive domains. We were also not able to rule out the potential effect of antipsychotic medication on ventricular volume, as patients were not antipsychotic naïve. However, we observed no correlation between treatment exposure and ventricular size within the patient group. Another factor to consider is our wide age of inclusion, with participants at the younger end of the range still undergoing important brain maturational changes. However, OCs are associated with an earlier age of onset (Baeza et al., 2021) thus we opted to include younger patients in order to increase the representativeness of the sample in terms of obstetric risk.

Our results suggest that difficulties during delivery might be important contributors to one of the most replicated correlates of psychosis, increased third ventricle volume. However, we observed no significant interaction between diagnosis and exposure to perinatal adversity. Difficulties during delivery were associated with larger ventricular volumes in both patients with FEP and HC. This is in keeping with the previously reported lack of an interactive effect between birth asphyxia and diagnosis on brain structure (Wortinger et al., 2020). Similarly verbal memory function was associated with third ventricular volume in both patients and controls. However, an additive risk of perinatal adversity and genetic predisposition has been suggested and, in our sample, FEP patients with difficulties during delivery had the largest third ventricle volume. Our findings thus further highlight the importance of peri-natal risk reduction interventions.

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