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Obstetric complications and cognition in schizophrenia: a systematic review and meta-analysis

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Review Article

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Abstract

Background. Schizophrenia (SZ) is a complex brain disorder linked to cognitive and neurostructural abnormalities that involves genetic and environmental factors with obstetric complications (OCs) at birth conferring a high risk for the disease. Indeed, current research in the general population describes the deleterious effect of OCs on cognitive performance in adulthood. With this rationale, we aim to review the relationship between OCs and cognition in SZ and related psychotic disorders.

Methods. A systematic review and meta-analysis describing cognitive function and OCs in patients with SZ and related disorders were conducted. PubMed, EmBase, SCOPUS, and the Cochrane Library were systematically searched to identify eligible studies up to January 2022. We calculated the effect sizes (Hedges' g) of cognitive domains within each study and quantified the proportion of between-study variability using the I^2 statistic. Homogeneity was assessed using the *Q*-statistic (X^2). The study was registered on PROSPERO (CRD42018094238).

Results. A total of 4124 studies were retrieved, with 10 studies meeting inclusion criteria for the systematic review and eight for meta-analysis. SZ subjects with OCs showed poor verbal memory [Hedges' $g = -0.89$ (95% CI −1.41 to −0.37), $p < 0.001$] and working memory performance [Hedges' $g = -1.47$ (95% CI −2.89 to −0.06), $p = 0.01$] in a random-effect model compared to those without OCs.

Conclusions. OCs appear to have a moderate impact on specific cognitive such as working memory and verbal memory. Our findings suggest that OCs are associated with brain development and might underlie the cognitive abnormalities described at onset of psychosis.

Introduction

Schizophrenia (Sz) is a complex brain disorder characterized by a wide array of symptoms, including delusions, hallucinations, disorganized behavior, and negative symptoms that together represent the diagnostic criteria for this unique disease (American Psychiatric Association, 2013). Although cognitive deficits have been long considered a core feature of SZ, they are not included in the DSM-5 or the ICD-10 criteria (Keefe & Fenton, 2007). Impairment in a broad range of cognitive domains has been consistently reported in individuals with SZ, including attention, working memory, verbal learning and memory, and executive functions (Bowie & Harvey, 2006). These deficits are moderate to severe and are present before the onset of frank psychosis (Davidson et al., 1999). In fact, different studies of neuropsychological functioning in ultra-high-risk subjects demonstrated cognitive impairments that were intermediate between healthy controls and patients with first-episode of psychosis (FEP) (Hambrecht, Lammertink, Klosterkötter, Matuschek, & Pukrop, 2002; Hawkins et al., 2004). Thus, neuropsychological deficits after a FEP appeared to remain stable over time (Bozikas & Andreou, 2011; Sánchez-Torres et al., 2018).

The developmental origins of health and disease (DOHaD) paradigm represents a framework that posits that environmental perturbations during the perinatal period or early life may lead to adverse health outcomes in adulthood (Gluckman & Hanson, 2006; Hanson & Gluckman, 2014). Among this environmental factors, obstetric complications (OCs) have been found to increase the risk of a plethora of chronic diseases, including mental health conditions such as psychosis (Cannon, Jones, & Murray, 2002; Davies et al., 2020; Garcia-Rizo & Bitanihirwe, 2020; Garcia-Rizo, Fernandez-Egea, Bernardo, & Kirkpatrick, 2015; O'Donnell & Meaney, 2017; Radua et al., 2018). Due to its heterogeneity, OCs could be at least described as difficulties during pregnancy and delivery with different outcomes (Mezquida et al., 2018), as suggested by Cannon (Cannon et al., 2002). Different difficulties during the perinatal period have long-lasting consequences on the cognitive profile of the general population, not only in childhood (Stålnacke, Tessma, Böhm, & Herlenius, 2019), but also, during adulthood (Flensborg-Madsen & Mortensen, 2017). Early prenatal and postnatal periods are extremely sensitive for the subsequent development of neuronal function and the programming of later behavior (Krugers & Joëls, 2014). For instance, preterm birth correlates with the later cognitive outcomes (Baron & Rey-Casserly, 2010; Mathewson et al., 2017). Similarly, hypoxic insults during mid- to late pregnancy have been reported to have a sex-specific effect on intelligence quotient (IQ) (Anastario, Salafia, Fitzmaurice, & Goldstein, 2012). As with brain morphology, cognition is also affected by the specific timing of the insult during brain development (Gee & Casey, 2015).

Specifically, patients with SZ show a higher prevalence of complications during the perinatal period (e.g. infections (Brown, 2006), maternal stress (Khashan et al., 2008) which beyond increasing the risk of psychiatric diagnosis also promote a diverse array of detrimental outcomes ranging from metabolic dysfunction (Garcia-Rizo & Bitanihirwe, 2020) and neuroimaging anomalies (Costas, Garcia-Rizo, Bitanihirwe, & Penades, 2020) to cognitive and clinical psychopathology (Mezquida et al., 2021). Indeed, these perinatal events might act as 'scars' which affect the brain in different pathways and so different abnormalities in functionality or structure might be expected (Insel, 2010). Thus, evidence suggests that, within patients with psychosis or related disorders, there is a relationship between the presence of OCs and poor cognitive performance in different domains (Borkowska & Rybakowski, 2002; Brown et al., 2011, 2009; Ellman, Yolken, Buka, Torrey, & Cannon, 2009; Gilvarry et al., 2000, 2001; Holthausen et al., 2002; Ochoa et al., 2013; Torniainen et al., 2013; Yurgelun-Todd & Kinney, 1993), even though results are heterogeneous. In fact, these cognitive disturbances, which sometimes are present at the time of onset of the first symptoms (Bora & Murray, 2014) might be somehow related to the presence of perinatal events.

In this context, our aim was to systematically review the available studies investigating the relationship between OCs and cognition in SZ and related psychotic disorders, using meta-analytic methods whenever possible. We hypothesized that OCs are related to even lower cognitive performance in patients diagnosed with SZ.

Materials and methods

Design

Data for the systematic review and meta-analyses were gathered in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol (PRISMA-P) checklist (Moher, Liberati, Tetzlaff, & Altman, 2009) (see online Supplementary Material 1). The review process has been registered with the international prospective register of systematic reviews (PROSPERO): 2018 CRD42018094238.

Literature search strategy

A systematic and computerized literature search was conducted in different scientific databases including Medline via Pubmed, EMBASE via OVID, SCOPUS, and the Cochrane Library.

The search strategy was performed using key terms relating to 'obstetric complications', 'cognition' and 'schizophrenia' or 'other psychotic disorders'. Reference lists of included articles were hand-searched for additional studies. A snowballing approach also was applied to identify additional studies meeting the inclusion criteria in the reference lists of studies that met the inclusion criteria. The full search strategy is described in online Supplementary Material 2.

Inclusion and exclusion criteria

The present study aimed to identify the literature focusing on the association between OCs and cognitive impairment in individuals with SZ and other psychotic disorders. We only included studies in which cognitive domains were evaluated in SZ patients with (cases) and without (controls) OCs. Included studies were published in English or Spanish, and on populations aged over 7 years old. We excluded commentaries, editorials, expert reviews, case reports, case series, or literature that did not provide novel information/research. No restrictions were placed on settings or time frames.

Papers published until the end of January 2022, and fulfilling the inclusion criteria were considered. If a study did not explicitly report data (e.g. expert opinions, comments, and editorials), we contacted the main authors to retrieve and ensure the quality of data.

Data extraction and quality assessment

Two independent reviewers (SA and MG) evaluated the identified articles. After all, potentially relevant studies were identified from each respective database; duplicates were removed using Mendeley software. Titles and abstracts of the remaining studies were screened. Firstly, MG independently screened studies with titles and abstracts and excluded those irrelevant to the research question. Whether a study's title suggested that it may contain relevant data/content, the abstract was assessed. Secondly, SA and MG assessed abstracts and excluded those which did not meet the inclusion criteria. Finally, whether the abstract indicated that the study provided information of relevance with regard to the effects of OCs on the cognition of SZ subjects, the full-text article of the study was read in its entirety to determine its eligibility. Then the suitability of these remaining full-text articles was subsequently evaluated, and so unrelated or nonapplicable studies were excluded following inclusion and exclusion criteria. During the process, discrepancies between the two reviewers were resolved by discussion with a third reviewer (CGR).

As with the eligibility phase, quality assessment was conducted by two authors (BB and CGR) using the Newcastle-Ottawa Scale (NOS) (Wells, Shea, O'Connell, & Peterson, 2000). This tool is divided into three sections that evaluate three quality parameters

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(selection, comparability, and outcome) divided across seven specific items.

Exposure and outcome measures

Exposure to OCs was defined as a wide range of events such as pregnancy complications, abnormal fetal growth, and delivery complications, which have already been related with an increased risk of SZ (Cannon et al., 2002). Since different methodologies have been described along the literature to describe the presence of a wide range of OCs, authors decided to include OCs data as a dichotomous variable: presence or absence of OCs. Additionally, seven studies have already been divided the groups according to the presence or absence of OC (Borkowska & Rybakowski, 2002; Brown et al., 2009, 2011; Gilvarry et al., 2000, 2001; Ochoa et al., 2013; Yurgelun-Todd & Kinney, 1993). Whether OCs data was reported on a continuous variable through scatter plot, we used a tool called WebPlotDigitizer to extract graphed data (Drevon, Fursa, & Malcolm, 2017). Then, we split the continuous variables using the cut-off of OCs according to the previous definition (Cannon et al., 2002). Besides, we combined two means and standard deviations into one mean and standard deviation when the authors reported different measures of dispersions for subjects with SCZ but with distinctive OCs (Altman, Machin, Bryant, & Gardner, 2000; Higgins et al., 2019).

The primary outcome was cognitive performance. It was grouped considering the most evaluated and affected domains in SZ (Bowie & Harvey, 2006), as follows:

(1) Verbal memory: Assessed with the California Verbal Learning Test (CVLT) (Delis, Kramer, Kaplan, & Ober, 1987) or 'Test Aprendizaje Verbal España-Complutense' [Complutense Spanish Verbal Learning Test] (TAVEC) (Benedet & Alexandre, 1998).
(2) Working memory: Assessed with the Letter-Number Sequencing Subtest of the Wechsler Adult Intelligence Scale (WAIS) (Wechsler, 1997) or Wechsler Intelligence Scale for Children (WISC) (Corral, Arribas, Santamaría, Sueiro, & Pereña, 2005) and Auditory N-back (2-back) test (Keefe & Fenton, 2007).
(3) Executive functions: Evaluated using the interference score from the Stroop test (Golden, 1978; Macleod, 1991) and Wisconsin Card Sorting Test (WCST) (Grant & Berg, 1948).
(4) Verbal fluency: Assessed with verbal fluency (category) and Thurstone word fluency test (Thurstone, 1938).
(5) Processing speed: Tested with the Trail Making Test, form A (TMT-A) (Reitan & Wolfson, 1995) and the Symbol Search subtest from WAIS.
(6) Attention: Tested with the Continuous Performance Test (CPT) (Conners, 2002) and the Digit Span Forward subtest of WAIS.
(7) IQ: Assessed with the National Adult Reading Test (NART) (Nelson, 1982) and with the Vocabulary subtest of WAIS/WISC-IV.

Statistical analyses

When adequate, a meta-analysis was performed using R software (version 4.1.0) and RStudio (version 1.4.1103) with packages 'meta' (version 4.17) and 'metafor' (version 2.4). We calculated effect sizes (Hedges' g) of cognitive domains within each included study comparing the means and standard deviation in subjects with SZ and OCs (cases) *v.* individuals with SZ without OCs (controls). The values are expressed as the mean Hedges' g across studies along with 95% confidence interval (CI). We calculated Hedges' g because it is appropriate for assessing bias in small sample size (Hedges & Olkin, 1985). A negative Hedges' g value means a poor performance of subjects with SZ exposed to OCs compared to nonexposed subjects with SZ. The effect size of Hedges' g was interpreted as follows: 0.2 = small, 0.5 = medium, and 0.8 = large. The neuropsychological assessments are highly heterogeneous; because of this, we will consider a random-effects model rather than the fixed-effect model, since the random-effects model is more conservative.

Additionally, we reported the I^2 statistic to quantify the proportion of between-study variability. Values of I^2 of 25%, 50%, and 70% were considered as small, moderate, and high proportions of heterogeneity, respectively (Higgins, Thompson, Deeks, & Altman, 2003). We tested homogeneity using the Q-statistic(X^2). The funnel plot was used for visual identification of bias or systematic heterogeneity. When there is no publication bias, all studies would lie symmetrically around the striped line (pooled effect size). After that, we performed Eggers' test to determine statistically the presence of publication bias (Egger, Smith, Schneider, & Minder, 1997). We considered a p value <0.05 significant in all statistical analysis.

Results

Study selection

The electronic database search yielded 4166 articles (see Fig. 1). Following the article screening of titles and abstracts, 22 full-text articles were obtained for detailed eligibility assessment. Full-text copies of those articles were obtained and when it was feasible, the authors were contacted directly for unpublished data and additional information. In this respect, five authors were contacted via e-mail and one author provided retrieved nonpublished data from the publication (Ochoa et al., 2013). Following this process, 10 articles were included for the qualitative assessment, and eight of which underwent meta-analysis (Borkowska & Rybakowski, 2002; Brown et al., 2011, 2009; Ellman et al., 2009; Gilvarry et al., 2000. 2001; Holthausen et al., 2002; Ochoa et al., 2013; Torniainen et al., 2013; Yurgelun-Todd & Kinney, 1993), while 12 were excluded due to a reason (see online Supplementary Material 3).

Quality assessment of the included studies showed that three studies were of high quality (score of >7 out of 9) and the remaining seven were of moderate quality (scoring 5 to 7 out of 9) (see Table 1). Inter-rater reliability between the reviewers on the NOS was evaluated by means of Cohen's kappa coefficient (κ), where the strength of κ was interpreted as follows: <0.20 poor; 0.21–0.40 fair; 0.41–0.60 moderate 0.61–0.80 substantial; 0.81–1.00 almost perfect (Altman, 1991). The overall interassessment agreement for total NOS scores was moderate ($\kappa = 0.57$).

Characteristics of included studies

A total of 693 subjects with SZ or related disorders were included across the different studies (range: 10–174), of which 37.95% (n = 263) presented with an OC. The main psychiatric diagnostic criteria applied were the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV). In terms of

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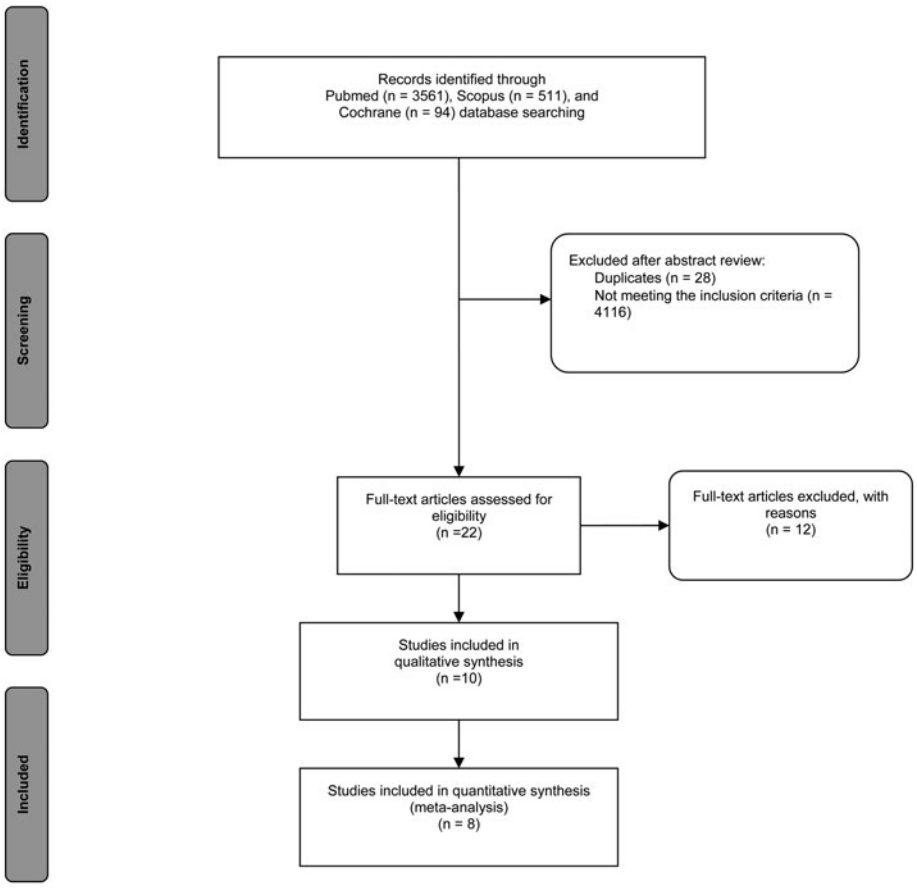

Fig. 1. PRISMA flow diagram. Presentation of the procedure of literature searching and selection with numbers of articles at each stage.

neurocognitive assessment, the most frequently evaluated domains were executive functioning (n of studies = 7) (Borkowska & Rybakowski, 2002; Brown et al., 2011, 2009; Holthausen et al., 2002; Ochoa et al., 2013; Torniainen et al., 2013; Yurgelun-Todd & Kinney, 1993), followed by attention ($n = 5$) (Brown et al., 2009; Ellman et al., 2009; Holthausen et al., 2002; Ochoa et al., 2013; Torniainen et al., 2013) and processing speed ($n = 5$) (Brown et al., 2011; Ellman et al., 2009; Holthausen et al., 2002; Ochoa et al., 2013; Torniainen et al., 2013). When exploring how OCs were measured, four articles used an objective measure such as birth weight (Torniainen et al., 2013) or maternal mother infection antibody testing (Brown et al., 2011, 2009; Ellman et al., 2009), while health records/registries, or patient/mother interview/scales were used in the other articles. See Table 1 for further details.

Qualitative synthesis of outcomes

Verbal memory

Two studies, one focusing on early onset of psychosis patients with a FEP (Ochoa et al., 2013) and another with chronic SZ (Brown et al., 2011), described that SZ patients who had experienced OCs performed worse in this domain compared to controls. A separate study of FEP and a second episode of psychosis patients did not find differences in OCs between those with normal cognition and those with cognitive impairment (Holthausen et al., 2002).

Working memory

Two of four studies (Ochoa et al., 2013; Torniainen et al., 2013) described an association between OCs and impaired working memory, while another (Brown et al., 2011) reported a trend for an association between maternal infection and the composite score for working memory ($p = 0.051$). Contrary, one study did not observe any such differences (Brown et al., 2009).

Executive function

Four of the seven studies that investigated the relationship between OCs and executive functioning showed an association between impaired executive performance and a history of OCs (Borkowska & Rybakowski, 2002; Brown et al., 2009; Ochoa et al., 2013; Torniainen et al., 2013). The three remaining studies did not observe such association (Brown et al., 2011; Holthausen et al., 2002; Yurgelun-Todd & Kinney, 1993).

Verbal fluency

None of the four studies that evaluated this domain reported differences between those patients with and without a history of OCs (Brown et al., 2011, 2009; Gilvarry et al., 2001; Holthausen et al., 2002).

Attention

The Five studies that evaluated attention described different results. attention found that patients with OCs had worse performance when evaluated by forward digits (Ellman et al., 2009; Torniainen et al., 2013) or CPT (Ochoa et al., 2013), while the other studies did not report any significant differences (Brown et al., 2009; Holthausen et al., 2002)

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Table 1. List and principal characteristics of included studies in the systematic review and meta-analysis

Authors, year Country	Study design	Population (Case/ Control)	Cognitive assessment	OC assessment	Risk of bias[a]	Main result
(Yurgelun-Todd & Kinney, 1993 USA)	Case-control	10 SZ patients (DSM-III-R) 8/2	WCST (perseverative errors)	Pregnancy and delivery complications (including specific types and timing of any labor-stimulating or anesthetic drugs, or use of obstetric procedures, such as forceps), and pediatric physical examinations	High (5 stars)	Perinatal OC and the number of perseverative errors on the WCST were positively correlated for the total sample, however, this correlation did not depend on the liability for SZ or other psychiatric illness. The correlation for SZ was not significant but slightly negative
(Gilvarry et al., 2000 UK)	Cross-sectional	Inpatients, 60 SZ (RDC) 17/43	NART	Lewis and Murray scale	Moderate (7 stars)	There was no significant difference in premorbid IQ between OC + and OC – patients
(Gilvarry et al., 2001 UK)	Nested case-control	Inpatient, 28 SZ (RDC) 9/19	NART; TVFT	Lewis and Murray scale	Moderate (7 stars)	There was no significant difference between OC + and OC- SZ patients before or after adjusting for IQ
(Borkowska & Rybakowski, 2002 Poland)	Prospective cohort	Inpatients, 50 SZ patients (DSM-IV) 32/18	TMT-B; WCST (perseverative errors; completed categories); Stroop B (Naming Color of Word-different)	Positive obstetric history was judged on account of the presence of serious illness of the patient's mother during pregnancy (e.g. diabetes, gestosis), intrauterine growth retardation, low Apgar score, low birthweight and perinatal complications	Moderate (6 stars)	WCST measures and TMT B were impaired in patients with OC compared to those without them
(Holthausen et al., 2002 Netherland)	Case-control	Outpatients, 118 SZ spectrum disorder (DSM-IV) 40/78	Computerized Spatial Working Memory Task; CPT; CVLT; Finger tapping test; Rey Complex Figure Test; Stroop; TMT-A, TMT-B, TMT-C; Verbal Fluency Tasks (category and letter)	Self-report questionnaire for the mother (pregnancy and birth OCs).	Moderate (6 stars)	There were no differences in OCs between those cognitively normal and those cognitively impaired
(Brown et al., 2009 USA)	Retrospective birth cohort	Outpatients, 24 SZ spectrum disorder patients (DSM-IV) 8/16	Auditory N-Back (0-back and 2-back d-prime); LNS; Ruff Figural Fluency (total correct); TMT-A and B; Verbal Fluency Test (Letter and Category fluency); WAIS-III Digit Span (Forward and Backward last correct) and LNS; WCST (total error, Perseverative errors, non-perseverative errors)	Prenatal infection (influenza antibody and/or toxoplasma IgG antibody)	Low (8 stars)	OC + patients committed significantly more total errors on the WCST and took significantly more time to complete the TMT-B. OC + patients also exhibited deficits on figural fluency, letter-number sequencing, and backward digit span
(Ellman et al., 2009 USA)	Prospective birth cohort	Outpatients, 111 psychotic patients (DSM-IV) 63/48	FIQ; PIQ; VIQ; WISC (information, vocabulary, comprehension, digit span, picture completion, block design and coding)	Third-trimester perinatal influenza exposure (IgG antibodies to influenza A and influenza B)	Low (8 stars)	OC + (exposure to influenza B) patients performed worse on the WISC subscales information and digit span than OC- patients

(Brown et al., 2011 USA)	Retrospective birth cohort	Outpatients, 25 SZ spectrum disorder patients (DSM-IV) 11/14	Auditory N-Back (0-back and 2-back d-prime); Executive function composite score; CVLT (trial 5 and total learning slope trials 1–5); Verbal Fluency Test (Letter and Category fluency); LNS; Ruff Figural Fluency (total correct); Verbal memory composite score; Symbol search; TMT-B; WAIS-III Digit Span (Forward and Backward last correct); Working memory composite score; WCST (total error, Perseverative errors, non-perseverative errors)	Maternal Genital / Reproductive infection (seropositivity to IgG antibody for HSV-2); physician diagnoses made during obstetric visits	Low (8 stars)	OC + patients performed more poorly on verbal memory, fine-motor coordination, and working memory than OC-
(Ochoa et al., 2013 USA)	Prospective cohort	Outpatients, 62 FEP (DSM-V) 43/19	CPT (omissions, commissions and processing speed index); Stroop test (interference and number of word); TAVEC and TAVECI (learning curve, immediate memory, long-term memory, recognition); TMT-A and B; WAIS-III/WISC-IV (digits, LNS, arithmetic and vocabulary)	Lewis and Murray scale	Moderate (6 stars)	OC + patients performed worse on TMT-B, learning curve of the TAVEC, Digit subtest of the WAIS and premorbid estimated IQ (vocabulary)
(Torniainen et al., 2013 Finland)	Retrospective birth cohort	Outpatients, 142 SZ patients (DSM-IV) 32/10	WAIS-R (Vocabulary, Similarities, Block Design and Digit Symbol subtests); TMT-A and B; Stroop test (interference); WMS-R (Digit Span Forward and Backward tasks and the Visual Span Forward and Backward tasks); CVLT (immediate recall, short delay recall and long delay recall)	Birth weight (OC + below 2500 gr or over 4000 gr)	Moderate (7 stars)	Both low and high birth weights were associated with lower performance in visuospatial reasoning, processing speed, set-shifting and verbal and visual working memory among persons with SZ compared to individuals with birthweight in the intermediate range

Cases, Schizophrenia spectrum disorder patients affected with an obstetric complication; Controls, Schizophrenia spectrum disorder patients without an obstetric complication; SZ, Schizophrenia; DSM, Diagnostic and Statistical Manual of Mental Disorders; SADS-L, Schedule for Affective Disorders and Schizophrenia, lifetime version; RDC, Research Diagnostic Criteria; FEP, First-episode psychosis; WCST, Wisconsin Card Sort Test; NART, National Adult Reading Test; TVFT, Thurstone's Verbal Fluency Test; TMT, Trail Making Test; CPT, Continuous Performance Task; CVLT, California Verbal Learning Test; WAIS, Wechsler Adult Intelligence Scale; LNS, Letter-Number Sequencing; FIQ, full scale IQ; PIQ, performance IQ; VIQ, verbal IQ; WISC, Wechsler Intelligence Scale for Children; TAVEC, 'Test Aprendizaje Verbal España-Complutense' [Complutense Spanish Verbal Learning Test]; TAVECI, 'Test Aprendizaje Verbal España-Complutense Infantil' [Complutense Spanish Verbal Learning Test for Children]; WMS, Wechsler Memory Scale; OC + , Patients who had been exposed to obstetric complications; OC-, Patients who had not been exposed to obstetric complications; BW, Birth Weight; HBW, High Birth Weight; LBW, Low Birth Weight; OC, Obstetric complication.

[a]Newcastle-Ottawa Scale.

Processing speed

Five articles assessed this domain. Two of them found evidence that OCs were associated with worse performance in processing speed (Ochoa et al., 2013; Torniainen et al., 2013), while the remaining three studies did not find such effects (Brown et al., 2009; Ellman et al., 2009; Holthausen et al., 2002).

Intellectual quotient

While Torniainen et al., found that there was not a significant difference between those patients with and without OCs (Torniainen et al., 2013), another article described a higher IQ for those who were not exposed (Ochoa et al., 2013). In a third study that used a prospective birth cohort with 111 psychotic patients, it was found that those exposed to influenza B had a nonsignificant reduction in IQ (as measured by WISC vocabulary subscale) (Ellman et al., 2009).

Quantitative synthesis of outcomes

The eight studies included in the meta-analysis comprised of 401 participants [median (interquartile range) participants per study, 39 (24.5–57.5)]. A total of 276 (90.49%) were male, but three studies did not report the frequencies of male subjects with SZ (Brown et al., 2011, 2009; Gilvarry et al., 2000).

SZ subjects with OCs showed poor verbal memory performance in the random-effect model compared to those without OCs [Hedges' $g = -0.89$ (95% CI −1.41 to −0.37), $p < 0.001$] (Fig. 2). Similarly, a worse neuropsychological performance in working memory was found in individuals with SZ and with OCs [Hedges' $g = -1.47$ (95% CI −2.89 to −0.06), $p = 0.01$].

In relation to random-effect models, there were no significant differences in executive function [Hedges' $g = 0.10$ (95% CI −0.19 to 0.39)], verbal fluency [Hedges' $g = -0.32$ (95% CI −0.79 to −0.15)], intellectual functioning [Hedges' $g = -0.45$ (95% CI −1.22 to 0.31)], processing speed [Hedges' $g = 0.19$ (95% CI −0.45 to 0.83)], and attention (Hedges' $g = 0.24$ (95% CI −0.17 to 0.64)) between subjects with a history of OCs and without OCs.

We detected high heterogeneity ($I^2 > 70\%$) in two of the evaluated cognitive domains: working memory [$X^2(2) = 10.74$, $p < 0.01$; $I^2 = 81\%$ (95% CI 42%–94%)], and intellectual functioning [$X^2(2) = 10.21$, $p < 0.01$; $I^2 = 80\%$ (95% CI 38%–94%)]. Nevertheless, other neuropsychological functions showed moderate ($I^2 > 50\%$ and $I^2 < 70\%$) or low ($I^2 < 50\%$) heterogeneity as executive function [$X^2(4) = 8.69$, $p = 0.07$; $I^2 = 54\%$ (95% CI 0%–83%)], processing speed [$X^2(2) = 4.23$, $p = 0.12$; $I^2 = 53\%$ (95% CI 0%–86%)], verbal memory [$X^2(1) = 0.07$, $p = 0.79$; $I^2 = 0\%$], verbal fluency [$X^2(2) = 0.88$, $p = 0.64$; $I^2 = 0\%$ (95% CI 0%–90%)], and attention [$X^2(3) = 4.92$, $p = 0.18$; $I^2 = 39\%$ (95% CI 0%–79%)]. There was no evidence of publication biases as indicated by visual inspection (online Supplementary Material 4a) and by the Egger test for small study effects (online Supplementary Material4b).

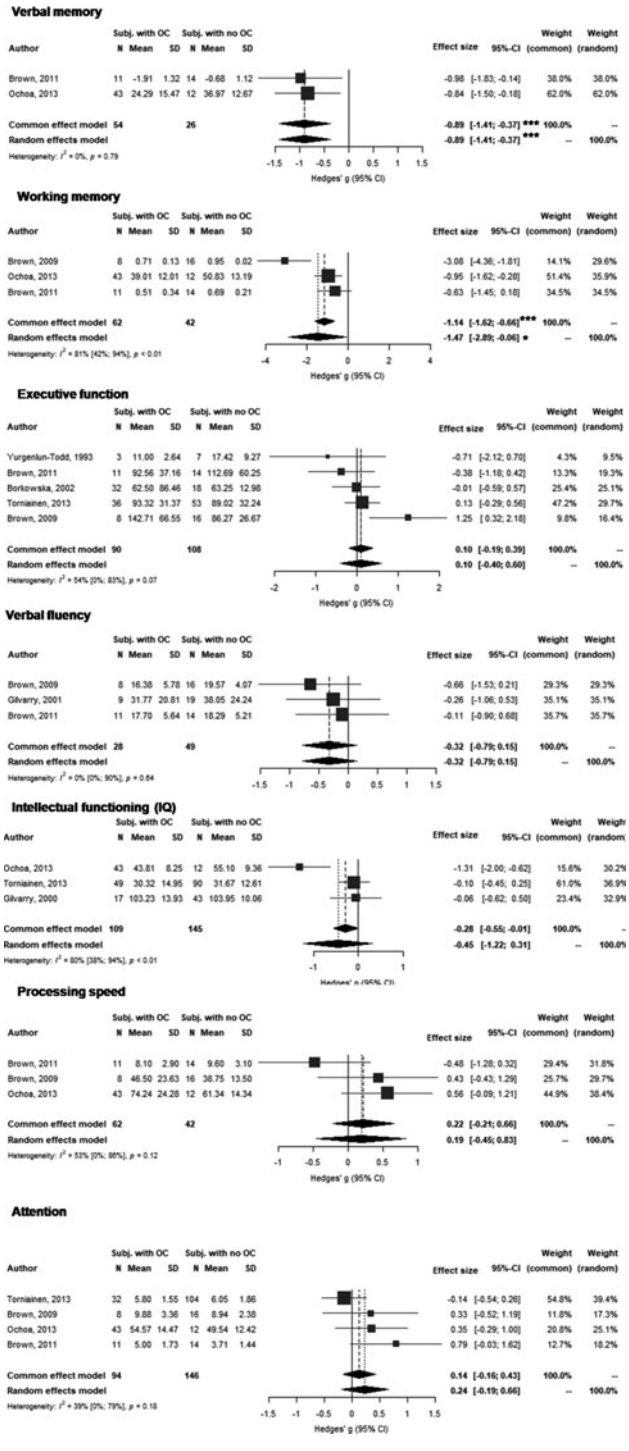

Fig. 2. Forest Plot of Cognitive Differences Between Patients With Schizophrenia With and Without Obstetric complications. Subj, Subjects; *$p < 0.05$: *** $p < 0.001$.

Discussion

The main findings of the present meta-analysis indicate that patients with SZ and OCs have cognitive deficits in working memory and verbal memory, in comparison to those SZ patients nonexposed to OCs and besides the few number of compared articles. To the best of our knowledge, this is the first systematic review and meta-analysis of the association between OCs and cognitive function in individuals with SZ and other psychotic disorders.

Although cognitive impairments across several domains have been reported in patients with SZ, our findings suggest that OCs were related to working and verbal memory. These cognitive domains have been considered a core cognitive deficit in SZ and have been proposed as endophenotypic markers (Park & Gooding, 2014) that are present at early phases of the illness, in

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ultra-high risk subjects and first episode psychosis patients (Brown et al., 2011; Sheffield, Karcher, & Barch, 2018). Indeed, verbal memory deficits may be an important risk marker for the development of schizophrenia-spectrum psychotic disorders (Lencz et al., 2006). Interestingly, cognitive difficulties have a great implication on the functionality of subjects with SZ while the literature suggests that cognitive dysfunction is associated with prominent functional impairment, which involves social, occupational, and independent living activities (Van Winkel et al., 2007). Verbal memory and working memory impairments have been also described as an important predictor of poor psychosocial functioning and everyday life (Faerden et al., 2013; Fett et al., 2011; Green, Kern, Braff, & Mintz, 2000; Hubacher et al., 2013; Puig et al., 2008; Tolman & Kurtz, 2012).

Unlike our results, four of the six included studies (Borkowska & Rybakowski, 2002; Brown et al., 2009; Ochoa et al., 2013; Torniainen et al., 2013) found an association between OCs and impaired executive function. Nevertheless, some aspects must be considered: first of all, the breadth of the concept of executive functions, and therefore, the large number of different assessment tools and their heterogeneity. Thus, while we have centered our analysis on inhibitory control (Stroop) and cognitive flexibility (WCST), there are others aspects of the executive functioning domain that remain unexplored (i.e. reasoning, problem solving, planning) (Diamond, 2013). Therefore, it might be more suitable to discuss techniques that assess different components of executive functions rather than functions *per se*. In consonance with our findings, none of the incorporated studies found significant results related to OCs and verbal fluency, neither phonological nor semantic. Interestingly, when evaluating figural fluency, it was significantly reduced in patients exposed to OCs compared to unexposed case subjects (Brown et al., 2011, 2009).

As regards to verbal memory, studies with both first and second episode of the psychosis population found no differences between subjects and controls (Holthausen et al., 2002; Ochoa et al., 2013), while in chronic SZ patients opposite results were found (Brown et al., 2011). A plausible explanation could be that, while we had focused our analysis in immediate memory, different results could have been obtained assessing the learning curve or delayed memory.

Opposite results have been found for processing speed: while some studies did not find significant results (Brown et al., 2009; Ellman et al., 2009; Holthausen et al., 2002), others described that OCs were related to slower performances (Ochoa et al., 2013; Torniainen et al., 2013). One possible explanation might be that certain factors, such as antipsychotic medication, relapse, severity of illness, among others, could influence processing speed (Knowles, David, & Reichenberg, 2010). For that reason, studies in naïve FEP patients in which the effect of some confounding factors such as chronicity or the influence of antipsychotic treatment are avoided, can be especially relevant. In a study on 62 FEP patients (both, early onset and adult onset) that evaluated OCs and were grouped according to their neurodevelopment contribution, patients with a higher prevalence of early environmental events presented a worse processing speed assessment evaluated with the TMT-A (Ochoa et al., 2013). Moreover, the difference in sample size could interfere in the results as well as how OCs were assessed. For example, Brown et al., assessed OCs by exposure to maternal infection (Brown et al., 2011, 2009), while others by birth weight or Lewis and Murray scale (Ochoa et al., 2013).

In regard to attention, our results did not find significant differences between patients with and without history of OCs. Previous literature has found conflicting results, some of them described worse performance on attention in patients with a history of an OC (Ochoa et al., 2013; Torniainen et al., 2013) while others have identified similar performance between groups (Brown et al., 2009). Even so, the complexity of the domain (viz., focused, selective, divided, alternating attention) as well as the heterogeneity of the tests might explain this result (Coubard, 2015).

Taking into account the existing published meta-analyses that provide support for the presence of OCs as a risk factor for SZ later in life (Cannon et al., 2002; Davies et al., 2020; Radua et al., 2018) and that our results suggest that OCs have been associated with verbal memory and working memory performance in patients with SZ, an exhaustive assessment of OCs would be recommended to tailor specific early intervention strategies. This point is relevant, because verbal memory has been extensively demonstrated as the best predictor of psychosocial functioning, so alterations in this domain are indicative of inadequate or very poor functioning in the community (Penadés & Gastó, 2010). Therefore, patients with OCs and FEP should be carefully followed up, and appropriate rehabilitation approaches could be designed.

Limitations

Several limitations should be taken into consideration when interpreting our results. These should be conceptualized according to the heterogeneity of the sample studied and the scarce number of retrieved articles. Besides, considering the small sample size of some of the manuscripts included, a main concern stems from the concept of OCs. Although in some studies OCs are grouped together (Gilvarry et al., 2000; 2001), literature and a critic review of the scales used (Cannon et al., 2002) suggest at least the need to differentiate between OCs during pregnancy and delivery with different outcomes (Mezquida et al., 2018), or even to differentiate between the intrauterine period, with difficulties during pregnancy or difficulties related to abnormal fetal growth or development (Cannon et al., 2002). Another important limitation which could have biased our results, is the timing of the event and the sex of the fetus (Ellman et al., 2019), with different responses to environmental exposure (Al-Qaraghouli & Fang, 2017). The intensity and duration of the adverse event as well as the time of exposure (duration and critical period) might also drive different outcomes (Graignic-Philippe, Dayan, Chokron, Jacquet, & Tordjman, 2014).

Although several cognitive domains are assessed in the context of the present study, some cognitive domains were not investigated at all (i.e. visual learning and memory or social cognition) or others were investigated by a smaller number of studies (i.e. just two studies included data on verbal memory).

Conclusion

Our results suggest that there is consistent evidence for a significant relationship between the presence of OCs and worse cognitive performance in two specific domains widely replicated to be altered in SZ, such as working memory and verbal memory, while a trend towards significance was observed in relation to IQ. However, no further statistical significance was described, probably due to the heterogeneity of the main risk factor studied, OCs. Nevertheless, these results confirm the effect of the perinatal period in the later development of cognitive disturbances in

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psychosis–present even at onset– and highlight a feasible common pathophysiological pathway (Bock, Wainstock, Braun, & Segal, 2015). However, as there were a limited number of studies to compare, further studies which specifically study the characteristics of perinatal stressful events are required to fully understand its impact on the cognitive function of patients affected by psychosis.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291722002409.

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Author contribution. Dr Amoretti analyzed and collected data while writing the manuscript in close collaboration with FD Rabelo-da-Ponte. FD Rabelo-da-Ponte verified and performed the analytical calculations and with Dr Amoretti wrote to the final version of the manuscript. Dr M Garriga conceived the study design, analyzed and collected data, and contributed to the final interpretation of the findings. M Florencia Forte contributed to the final interpretation of the findings. while provided a critical review and developed the theoretical formalism. Dr R Penadés, Dr E Vieta, Dr E. Parellada, Dr J Antoni Ramos-Quiroga, Dr CS Gama and Dr N Verdolini provided critical review and developed the theoretical formalism. Dr B Bitanihirwe analyzed and collected data while providing a critical review and developed the theoretical formalism. Dr C Garcia-Rizo conceived of the presented idea, analyzed data, and supervised the progression and findings of this work. All authors discussed the results and contributed to the final manuscript.

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