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PRENATAL INFECTION AND EXECUTIVE DYSFUNCTION IN ADULT SCHIZOPHRENIA

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Abstract

Objective—Executive dysfunction is one of the most prominent and functionally important cognitive deficits in schizophrenia. Although strong associations have been identified between executive impairments and structural and functional prefrontal cortical deficits, the etiological factors that contribute to disruption of this important cognitive domain remain unclear. Increasing evidence suggests that schizophrenia has a neurodevelopmental etiology, and several prenatal infections have been associated with risk of this disorder. To date, however, no previous study has examined whether in utero infection is associated with executive dysfunction in patients with schizophrenia.

Method—In the present study, we assessed the relationship between serologically documented prenatal exposure to influenza and toxoplasmosis and performance on the Wisconsin Card Sorting Test (WCST) and the Trail Making Test, part B (Trails B), as well as other measures of executive function, in 26 patients with schizophrenia from a large and well-characterized birth cohort.

Results—Cases who were exposed in utero to infection committed significantly more total errors on the WCST and took significantly more time to complete the Trails B than unexposed cases. Exposed cases also exhibited deficits on figural fluency, letter-number sequencing, and backward digit span.

Conclusion—Prenatal infections previously associated with schizophrenia are related to impaired performance on the WCST and Trails B. The pattern of results suggests that cognitive set-shifting ability may be particularly vulnerable to this gestational exposure. Further work is

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necessary to elucidate the specificity of prenatal infection to these executive function measures and examine correlates with neuroanatomic and neurophysiologic anomalies.

Introduction

Among the wide range of neurocognitive deficits that characterize schizophrenia, executive dysfunction is one of the most prominent and functionally important(1;2). Executive dysfunction expresses itself as impaired reasoning and problem-solving and an inability to use appropriate contextual information to generate and implement adaptive behaviors(3). Not surprisingly, executive dysfunction is associated with more severe and disabling forms of schizophrenia as well as poorer functional outcome(2). A large body of research has identified a strong association between executive impairments and structural and functional deficits in the prefrontal cortex(4;5); however, our field still lacks a clear understanding of the etiological factors that contribute to disruption of this functionally important cognitive domain.

Increasing evidence suggests that schizophrenia has a neurodevelopmental etiology. Exposure to prenatal infections and to other obstetric complications (OCs) are neurodevelopmental insults that increase vulnerability to this disorder(6–9). For example, in a birth cohort in northern California followed up for schizophrenia in adulthood, the Prenatal Determinants of Schizophrenia (PDS) sample(10), we demonstrated that serologically documented exposure to early to mid-gestational influenza(11) and elevated toxoplasma antibody(12) are associated with schizophrenia.

To date, only a few previous studies have directly investigated the relationship between neurodevelopmental risk factors and cognitive deficits in schizophrenia. In those studies, OCs, obtained from birth records, were associated with perseverative errors on the Wisconsin Card Sorting Test (WCST), a measure of cognitive set-shifting and concept formation, in both adult patients with schizophrenia(13;14) and in healthy subjects(15). In an additional study, the combination of OCs and poor performance on Part B of the Trail Making Test (Trails B) discriminated patients with schizophrenia from healthy comparison subjects, including unaffected siblings of schizophrenia patients(16). These studies were limited, however, by the use of clinical, rather than population-based samples; by the use of hospital records to identify OCs, rather than systematically collected prospective data; by heterogeneous definitions of “obstetric complications”; and by incomplete data on prenatal complications. One common OC that may have accounted for at least some, if not a considerable degree, of the observed effects is prenatal infection. However, in utero infection was not documented by serologic biomarkers. Hence, we used prospective data from a population-based birth cohort to test the hypothesis that serologically documented prenatal infections associated with schizophrenia in our previous studies would be related to impaired performance on the two measures of executive function previously reported as having associations with obstetric complications (WCST and Trails B). The sample comprised subjects from the PDS study who were recruited for the Developmental Insult and Brain Anomaly in Schizophrenia (DIBS) study, which included a comprehensive neurocognitive assessment performed on clinically stable adult subjects. We also investigated whether in utero infection was associated with other executive function processes in secondary analyses. Although we postulated that prenatal infection would affect neuropsychological performance in both SSD cases and controls, we restricted the analyses to SSD cases only, due to an insufficient number of exposed controls.

Methods

Description of the cohort

The subjects were derived from the PDS sample, which has been fully described in a previous publication(10), and will therefore be only briefly summarized here. The mothers of the cohort members were enrolled in the Child Health and Development Study (CHDS) (17), which occurred from 1959–1966. During that period, the CHDS recruited nearly every pregnant woman receiving obstetric care from the Kaiser Permanente Medical Care Plan (KPMCP) in Alameda County, California. Hence, all offspring were automatically enrolled in KPMCP. This cohort consisted of the subsample of 12,094 live births who were members of KPMCP from 1981, the beginning of case ascertainment, through 1997, the end of follow-up. Subjects who remained in KPMCP and subjects lost to follow-up did not differ from one another on several characteristics(10;18).

Collection of maternal sera

A unique feature of the CHDS was the collection of maternal serum during pregnancy and storage at -20 degrees C(10).

Serologic measures

The assay methods are described in previous publications (11;12) and are largely reiterated here.

Influenza assay procedure—The antigens comprised those of the prevalent influenza strains from 1959–1966 in northern California, including A/H2N2/Japan/57, A/H2N2/Japan/62, A/H2N2/Taiwan/64, and B/Massachusetts/66. The hemagglutination inhibition (HAI) method, following GLP standards as previously described (19;20), was used to assay the sera for antibody to influenza.

Influenza infection was defined as the first occurrence during pregnancy of an influenza antibody titer ≥ 20 . In accord with Brown et al (11), influenza exposure was classified as influenza infection from day 0 post-LMP until day 142 post-LMP (the midpoint of pregnancy).

Toxoplasmosis laboratory assay—In accord with an established protocol(21), toxoplasma IgG antibody titers were determined by the screen agglutination test, followed by the Sabin-Feldman dye test(22), the reference standard (23). All dye test IgG titers $< 1:16$ are considered negative. In keeping with our previous finding(12), exposure was defined as a toxoplasma IgG antibody titer of $\geq 1:128$. The tested samples represented the last serum specimen available for each pregnancy, all of which were either third trimester or perinatal.

Due to the modest number of cases exposed to each of the two infections during pregnancy, we defined serologic exposure for the present study as either an influenza titer ≥ 20 during the first half of gestation or a toxoplasma IgG titer $\geq 1:128$. No cases met criteria for exposure to both infections. Two cases missing prenatal sera were not included in the analysis.

Ascertainment and diagnosis of cases of SSD in the PDS sample

These methods are elaborated in detail in previous publications(10;11), and are summarized here. The main outcome was schizophrenia and other schizophrenia spectrum disorders (SSD), defined as: schizophrenia, schizoaffective disorder, delusional disorder, psychotic disorder not otherwise specified, and schizotypal personality disorder, in accord with previous studies (24). Case ascertainment and screening were based on computerized record

linkage between the CHDS and KPMCP identifiers from inpatient, outpatient, and pharmacy registries. Potential cases (patients with diagnoses including ICD-9 codes of 295–299 and/or patients treated with antipsychotics) were administered the Diagnostic Interview for Genetic Studies (DIGS) (25) by clinicians with at least a master's degree in a mental health field, trained to reliability. Psychiatric diagnoses (DSM-IV) were made following consensus of three experienced research psychiatrists based on the DIGS and psychiatric/medical records. Chart review by experienced clinicians was used for potential cases who were not interviewed, and all diagnoses were confirmed by a research psychiatrist. These procedures yielded 71 total SSD cases, 44 interviewed with the DIGS, and 27 diagnosed by chart review. Among these 71 SSD cases, 64 had available prenatal sera. There were 38 cases with schizophrenia, 15 with schizoaffective disorder (83% schizophrenia/schizoaffective disorder), and 11 with other schizophrenia spectrum disorders.

Ascertainment of comparison subjects

Selection of comparison subjects began with exclusion of the SSD cases already diagnosed and 318 subjects with major psychiatric disorders other than SSD. Comparison subjects were matched 1:1 to the cases on membership in KPMCP at the time of case ascertainment, date of birth, sex, and availability of maternal sera (10).

Ascertainment of the DIBS sample

The DIBS is a nested case-control study. All PDS cases and comparison subjects matched 1:1 for neuropsychological assessments who met eligibility criteria were targeted. Exclusion criteria for both cases and controls were as follows: diabetes, hypertension, history of heart disease, HIV/AIDS, cancer, autoimmune disorders, cerebrovascular disease, brain tumor, multiple sclerosis, any neurodegenerative disorder, mental retardation, epilepsy/seizures, meningitis/encephalitis, Tourette's disorder, autism/other pervasive developmental disorders, Parkinson's disease, tardive dyskinesia, head trauma with loss of consciousness. Cases who were currently hospitalized or deemed to be too severely psychotic for neurocognitive testing based on family report were also excluded. For controls only, exclusion was also made based on a history or current treatment of an Axis I psychiatric disorder (DSM-IV criteria), except for adjustment disorder. These cases and controls were recruited in tandem with an additional protocol, which excluded individuals on the basis of obesity (>300 pounds), and thus this criterion was applied to the protocol of the present study (only 2 subjects, 1 case and 1 control, were excluded based on this criterion). Selection of subjects was not determined by maternal antibody titer.

Subjects were recruited using updated information from the PDS study. The flow diagram (Figure 1) depicts the recruitment and selection of cases and controls in the neuropsychological component of the DIBS study. Twenty six cases of schizophrenia and other schizophrenia spectrum disorders (13 with schizophrenia, 7 with schizoaffective disorder and 6 with other schizophrenia spectrum disorders) and 24 controls were enrolled and completed the neuropsychological assessments detailed in the next section.

All subjects provided written informed consent. The study protocol was approved by the Institutional Review Boards of the New York State Psychiatric Institute, the Kaiser Foundation Research Institute, the University of California, San Francisco, and the San Francisco Department of Veterans Affairs Medical Center.

Neuropsychological assessments

Graduate students (minimum of master's level) in a mental health-related field were trained by WSK and JP in the administration and scoring of the neuropsychological tests. Detailed manuals were used to maximize inter-rater reliability for both test administration and

scoring. The neuropsychological battery included: Wisconsin Card Sorting Test (WCST), Trail Making Test Parts A and B (Trails A, Trails B), Verbal fluency (letter, category), Ruff Figural Fluency Test (figural fluency), Wechsler Adult Intelligence Scale (WAIS-III) Digit Span, forward total (digits forward) and backward total (digits backward), Wechsler Memory Scale (WMS-III), Letter-Number Sequencing, Auditory N-back (2-back, 0-back), and the reading subtest of the Wide Range Achievement Test-Version III (WRAT-III reading). These tests have been described in detail elsewhere(26;27). Selection of the WCST and Trails tests was based on previous studies on relationships between OCs and performance on these measures (13–15), while selection of the remaining tests was based on their capacity to test other aspects of executive function and working memory performance relevant to schizophrenia. The WRAT-III reading subtest was included as an estimate of overall premorbid cognitive ability(27;28).

Analytic method

Two primary sets of statistical comparisons were made: 1) cases vs. controls; and 2) prenatal infection-exposed vs. unexposed cases. The second of these analyses was restricted to the cases because there were too few exposed controls to permit a meaningful analysis of the data.

Prior to conducting these analyses, demographic variables were dichotomized and compared by chi-square tests. Table 1 presents comparisons between cases exposed and unexposed to serologically documented infection. The groups were similar with respect to maternal age, race, education, and parity.

We observed unequal variances for certain response variables in both the comparisons between cases and controls and between prenatal infection-exposed and unexposed cases (see Tables 3–5). Non-parametric methods were considered; however, the sample size was insufficient to use these methods without sacrificing statistical power. While a weighted least squares approach could possibly address unequal variances, specification of these weights is difficult in practice. Consequently, we adopted a new method, namely generalized linear models (GLM) (29). GLM is a flexible parametric class of models suitable for small datasets in which the conditional distribution of the response given the predictors is chosen from an exponential family (for example, Gaussian, binomial, Poisson, gamma) and can exploit specific structure in the response variables of the study. The variance structure is determined by the particular GLM, with only the Gaussian model having constant variance. For WCST total errors as the response, a binomial regression model with 47 trials provides a reasonable approximation because the test itself is based on 47 questions, each with a binary outcome; similarly, binomial regression is applicable for the analysis of Digit Span and Letter-Number Sequencing, the number of trials being given in Tables 3 and 5. For the Trail Making Test, gamma regression is suitable, as the response is time in seconds. For the Verbal fluency test, Poisson regression is appropriate since there is no theoretical limit to the number of correct responses. Finally, for the Auditory N-back, in which the response is a standardized continuous measurement, a Gaussian model was used. All analyses were also adjusted for WRAT-III reading scores in an effort to equate individuals on premorbid cognitive ability. In terms of the effect of the exposure on WRAT-III reading, there was no significant difference ($p=.19$) between the groups [exposed (mean, SD)=98.1, 11.4); unexposed (mean, SD)=90.6, 13.4], but the mean difference of 7.5 points suggested that this could represent a meaningful difference. Moreover, this difference could obscure executive function differences between groups since the exposed group displayed higher WRAT-III scores, yet exposed cases would be expected to have poorer executive function than the unexposed cases. Therefore, cognitive measures were compared after controlling for WRAT-III reading.

Statistical significance was based on $p < .05$; all tests were two-tailed. Effect sizes can be assessed by inspecting the confidence intervals for the regression parameter corresponding to exposure (see Tables 3–5).

Results

Comparison of DIBS cases and non-DIBS PDS cases

Table 2 presents comparisons between PDS cases who participated, and who did not participate, in the DIBS study. There were no differences between the groups on maternal age, race, education, and parity. Although not the focus of this paper, we also compared these demographic variables between PDS controls who did and did not participate in the DIBS. There were no differences on any of these demographic variables (all p values $> .60$).

Comparison of executive function measures between schizophrenia cases and matched controls

We first compared performance on measures of executive function and working memory between schizophrenia cases and controls in order to validate our findings against those documented in the literature. As expected, cases performed significantly worse than controls (Table 3). The differences reached statistical significance for nearly all tests.

Comparison of WCST and Trails B measures between schizophrenia cases exposed and unexposed to in utero infection (Primary analyses)

Cases exposed in utero to infection committed significantly more total errors on the WCST ($p < .001$). Exposed cases took significantly more time to complete the Trails B than unexposed cases ($p = .001$). There were, however, no differences between exposed cases and unexposed cases on time to complete the Trails A, a measure of psychomotor processing speed ($p = .376$) (Table 4).

Comparison of other executive function measures between schizophrenia cases exposed and unexposed to in utero infection (Secondary analyses)

Exposed and unexposed cases did not differ significantly on performance on any of the other neuropsychological measures, except for figural fluency, which was significantly reduced for exposed compared to unexposed cases ($p < .001$) (Table 5). There were also statistical trends for digits backward ($p = .097$) and letter-number sequencing ($p = .077$), indicating poorer performance in exposed compared with unexposed cases.

The results were similar when the sample was restricted to schizophrenia or schizoaffective disorder cases. Cases exposed to in utero infection evidenced more total errors ($p < .001$) on the WCST [mean (SD) = 19.4 (16.3)] compared to unexposed cases [mean (SD) = 12.8 (8.6)] ($p < .001$). Time to complete the Trails B was significantly longer ($p = .002$) in the exposed [mean (SD) = 153.4 (64.1)] compared to the unexposed [mean (SD) = 98.7 (21.4)]. Time to complete the Trails A did not differ ($p = .843$) between the exposed [mean (SD) = 49.7 (23.6)] and unexposed [mean (SD) = 43.3 (13.1)]. For the additional neuropsychological tests, the results for schizophrenia and schizoaffective disorder cases were similar to the full SSD sample (results available upon request).

Discussion

To our knowledge, these data represent the first demonstration of an association between in utero infection and cognitive dysfunction in schizophrenia. Consistent with our hypothesis, cases who were serologically documented with in utero exposure to influenza or to elevated toxoplasma IgG antibody performed significantly more poorly than unexposed cases on the

WCST and on Trails B. Strengths of the study include a well-characterized, representative cohort and direct, prospectively acquired biomarkers of infection.

As noted in the Introduction, three previous studies have specifically examined the relation of OCs to WCST and Trails B performance. In the first study, schizophrenia cases with a history of OCs committed more perseverative errors on the WCST than cases without OCs (13). In the second study, OCs were correlated with perseverative errors on the WCST in healthy subjects (15). However, the types of prenatal complications included in the analyses of that study were heterogeneous and were based solely on medical records from hospitals, rather than on data from prenatal sera. Although no correlation was found between perinatal OCs and WCST performance in schizophrenia cases in the latter study, the patient sample consisted of only 10 subjects, limiting statistical power, as noted by the authors. In contrast, there were considerably more patients with schizophrenia in the present study. In a third study, a marked and statistically significant increase in the co-occurrence of poor Trails B performance and the presence of at least one OC was reported in schizophrenia cases, compared to controls (16). While that study did not directly test for an association between perinatal OCs and Trails B performance, the finding is consistent with the present results.

Examination of the pattern of results raises several questions. First, we consider whether the findings of impaired performance in exposed cases on Trails B and other executive function measures can be attributed to a psychomotor processing speed deficit. This seems unlikely because we observed no difference between exposed and unexposed cases on Trails A time. A second question is whether the results might be explained by greater problems in abstraction and concept formation in exposed cases, as these neurocognitive abilities are required for WCST performance; however, the Trails B test does not require concept formation.

Third, we consider an association between prenatal infection and working memory performance, a domain assessed in the secondary analyses. In this regard, a statistical trend was observed for diminished performance on digits backward, suggesting a deficit in storage or manipulation of information in working memory. There was also a statistical trend for a decrement in performance on letter-number sequencing, a task which places greater demands on information manipulation in working memory than digits backward. No deficits were observed, however, on digits forward, which tests simple short-term memory storage, and on the auditory N-back test, which is most strongly related to working memory updating. Hence, there are suggestions that certain components of working memory may have been disrupted by prenatal infection.

The findings of the secondary analyses were also somewhat inconsistent for fluency. Exposure to infection was associated with a significant decrement in performance on figural fluency, and a moderate though nonsignificant disruption in category fluency but there were no group differences in letter fluency.

Set-shifting is a common neurocognitive function required for performance on both the WCST and Trails B. This function refers to the ability to switch mental sets in order to perform a given task. In contrast, the executive functions examined in our secondary analyses do not have a set-shifting component. Thus, these and previous findings (15;16) suggest that this neuropsychological function may be particularly vulnerable to the effects of prenatal and perinatal insults on the developing brain.

The relevance of these findings to the pathogenesis of schizophrenia is underscored by the fact that to date, there are no established etiologies of neurocognitive function in this disorder. There is, however, evidence that certain genetic polymorphisms may be related to several of the cognitive impairments observed in schizophrenia (30;31). The present study

suggests that environmental insults which occur during the prenatal period, and which have been associated with risk of schizophrenia, may similarly lead to cognitive vulnerability. Combined with preclinical studies, these results may lead to an improved understanding of the etiopathogenic pathways that account for disruptions in specific aspects of executive function, and suggest potential strategies aimed at preventing and treating these impairments.

We note several limitations to this study, the first being that we utilized a proxy measure of influenza exposure; however, as previously described(11), this measure was well-validated against seroconversion. Second, due to the modest sample size, it is possible that the absence of statistically significant associations between prenatal infection and certain executive function measures in our secondary analyses may have been due to insufficient statistical power; thus, larger samples will be necessary to confirm the present findings. Third, we were not able to assess whether the observed effects were specific to schizophrenia, due to the lack of a sufficient number of serologically documented exposed healthy comparison subjects and to the absence of a psychiatric comparison group.

Conclusion

We have demonstrated that prenatal infection is associated with considerably impaired performance on the Wisconsin Card Sorting Test and the Trailmaking Test, Part B, both of which were shown previously to be related to perinatal obstetric complications. In contrast to those previous studies, the present investigation featured a well-characterized, representative birth cohort and direct, prospective biomarkers of infection. The pattern of findings suggests that cognitive set-shifting ability may be particularly vulnerable to this gestational exposure. Future work is necessary to assess whether these findings are also present in controls, to further examine specificity to these executive function measures, and to assess whether prenatal infection is associated with neuroanatomical or neurophysiological anomalies in schizophrenia that may be related to the observed disturbances. Moreover, we shall examine additional types of OCs to assess whether they have similar effects on neurocognitive and other outcomes, which may suggest shared or distinct underlying mechanisms.

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Figure 1. Flow diagram of the selection of cases and controls for the Developmental Insult and Brain Anomaly in Schizophrenia (DIBS) Study.

Figure 2. Prenatal serologic infection and performance on the Wisconsin Card Sort Test in schizophrenia/schizophrenia spectrum disorder cases^{a, b}

^an=8 exposed, 16 unexposed

^bsignificant difference between exposed and unexposed groups, $p < 0.001$

Figure 3. Prenatal serologic infection and performance on the Trails B in schizophrenia/schizophrenia spectrum disorder cases^{a, b}

^an=8 exposed, 16 unexposed

^bsignificant difference between exposed and unexposed groups, $p < 0.001$

Table 1

Prenatal serologic infection and demographic variables in schizophrenia/schizophrenia spectrum disorder cases

	Exposed Cases N=8	Unexposed Cases N=16	Proportion exposed within each category	
Maternal age^a	N	N	%	p
≤ 29 yrs	4	9	30.8	1.000
> 29 yrs	4	7	36.4	
Maternal race				
White	4	10	28.6	.796
Black	3	5	37.5	
Other	1	1	50.0	
Maternal education^b				
≤ High school grad/trade school	5	11	31.3	1.000
Some college/college grad/RN	2	5	28.6	
Maternal parity				
0 or 1 prior livebirths	3	8	27.3	.680
2 or more prior livebirths	5	8	38.5	

^a Median maternal age is 29 years

^b N missing values: n=1 exposed case

Characteristics of PDS schizophrenia/schizophrenia spectrum disorder cases who participated and did not participate in the DIBS

Table 2

	DIBS Cases N=26		Non-DIBS PDS Cases N=45		P
Maternal age ^{a, b}	N	%	N	%	
≤29 yrs.	15	57.7	27	61.4	.804
>29 yrs.	11	42.3	17	38.6	
Maternal race ^b					
White	14	54.0	20	45.0	.608
Black	10	38.0	22	50.0	
Other	2	8.0	2	5.0	
Maternal education ^c					
≤ High school grad/trade school	16	66.7	25	65.8	1.000
Some college/college grad/RN	8	33.3	13	34.2	
Maternal parity					
0 or 1 prior livebirths	12	46.2	22	48.9	1.000
2 or more livebirths	14	53.8	23	51.1	

^aMedian maternal age is 29 years

N missing values:

^bn=1 Non-DIBS PDS Case;

^cn= 2 DIBS cases, n= 7 Non- DIBS PDS Cases

Table 3

Performance on executive function measures in schizophrenia/schizophrenia spectrum disorder cases and matched controls in DIBS sample

	Cases N=26		Controls N=24		p ^a	Parameter 95% CI	Generalized Linear Model Used
	Mean	SD	Mean	SD			
Wisconsin Card Sort Test (WCST)							
Total errors	14.96	11.62	6.42	5.73	<.001	(.752, 1.189)	Binomial with 47 trials
Perseverative errors	5.62	6.78	1.67	2.46	<.001	(.858, 1.608)	Binomial with 46 trials
Non-perseverative errors	9.35	6.88	4.75	3.70	<.001	(.429, .934)	Binomial with 47 trials
Trail Making Test							
Trails B time (sec.)	104.39	50.79	52.92	12.36	<.001	(-.012, -.006)	Gamma
Trails A time (sec.)	41.73	17.46	22.63	5.39	<.001	(-.028, -.015)	Gamma
Verbal Fluency Test							
Letter fluency (total correct)	12.23	3.67	14.46	2.96	.073	(-.311, .014)	Poisson
Category fluency (total correct)	18.20	5.23	22.42	5.50	.002	(-.341, -.075)	Poisson
Ruff Figural Fluency Test (total correct)	61.89	24.09	89.25	28.65	<.001	(-.412, -.274)	Poisson
WAIS Digit Span							
Forward total	9.23	2.66	10.54	1.98	.173	(-.518, .093)	Binomial with 16 trials
Backward total	5.89	2.03	7.17	2.35	.382	(-.462, .177)	Binomial with 14 trials
Letter-Number Sequencing	7.69	2.90	10.21	3.02	.014	(-.591, -.067)	Binomial with 21 trials
Auditory N-back							
Two-back d-prime	0.62	0.28	0.81	0.15	.047	(-.277, -.002)	Gaussian
Zero-back d-prime	0.92	0.13	0.94	0.05	.293	(-.099, .030)	Gaussian

^a Adjusted for WRAT III reading and based on appropriate Generalized Linear Model with canonical link.

Prenatal serologic infection and performance on executive function measures in schizophrenia/schizophrenia spectrum disorder cases: Primary analyses

Table 4

	Exposed Cases N=8		Unexposed Cases N=16		p ^a	Parameter 95% CI	Generalized Linear Model Used
	Mean	SD	Mean	SD			
Wisconsin Card Sort Test (WCST)							
Total errors	21.00	15.72	11.94	8.70	<.001	(.843, 1.410)	Binomial with 47 trials
Perseverative errors	7.25	8.86	4.25	5.25	<.001	(.459, 1.264)	Binomial with 46 trials
Non-perseverative errors	13.75	9.27	7.69	4.77	<.001	(.605, 1.233)	Binomial with 47 trials
Trail Making Test							
Trails B time (sec.)	142.71	66.55	86.27	26.67	.001	(-.008, -.002)	Gamma
Trails A time (sec.)	46.50	23.63	38.75	13.50	.376	(-.012, .005)	Gamma

^a Adjusted for WRAT III reading and based on appropriate Generalized Linear Model with canonical link.

Prenatal serologic infection and executive function in schizophrenia/schizophrenia spectrum disorders cases: Secondary analyses

Table 5

Verbal Fluency Test	Exposed Cases N=8		Unexposed Cases N=16		p ^a	Parameter 95% CI	Generalized Linear Model Used
	Mean	SD	Mean	SD			
Letter fluency (total correct)	13.00	4.04	12.44	3.35	.958	(- .240, .253)	Poisson
Category fluency (total correct)	16.38	5.78	19.57	4.07	.122	(- .379, .045)	Poisson
Ruff Figural Fluency Test (total correct)	51.75	22.99	69.81	21.25	<.001	(- .497, -.264)	Poisson
WAIS Digit Span							
Forward total	9.88	3.36	8.94	2.38	.768	(- .386, .522)	Binomial with 16 trials
Backward total	5.38	1.06	5.94	2.41	.097	(- .910, .076)	Binomial with 14 trials
Letter-Number Sequencing	7.25	3.77	8.13	2.55	.077	(- .773, .040)	Binomial with 21 trials
Auditory N-back							
Two-back d-prime	0.71	0.13	0.57	0.30	.471	(- .149, .311)	Gaussian
Zero-back d-prime	0.93	0.06	0.95	0.02	.410	(- .052, .022)	Gaussian

^a Adjusted for WRAT III reading and based on appropriate Generalized Linear Model with canonical link