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Low maternal hemoglobin during pregnancy and diminished neuromotor and neurocognitive performance in offspring with schizophrenia

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ABSTRACT

Objective: Previous research has linked maternal anemia during pregnancy with increased risk for schizophrenia in offspring. However, no study has sought to determine whether this early insult leads to a more severe form of the disorder, characterized by worsened motor and neurocognitive functioning.
Method: Subjects were 24 cases diagnosed with schizophrenia and 22 controls from the Developmental Insult and Brain Anomaly in Schizophrenia (DIBS) study. Hemoglobin values were measured throughout pregnancy. Among offspring, psychiatric diagnoses were determined through semi-structured interviews and medical records review and comprehensive neurocognitive assessment batteries were conducted in adulthood.
Results: Results indicated that among cases decreases in maternal hemoglobin led to significant decreases in scores on the Grooved Pegboard test, the Finger Tapping test and the Wechsler Adult Intelligent Scales (WAIS) information subtest. In contrast, controls only exhibited decreases in performance on the California Verbal Learning Test (CVLT) long-delay recall after fetal exposure to lower hemoglobin. There were also significant interactions between hemoglobin and case status for all of the motor tasks.
Conclusions: These findings support the hypothesis that fetal exposure to decreases in maternal hemoglobin is related to preferentially poorer neuromotor function among cases compared to controls, as well as general intellectual difficulties among cases. Controls were relatively unaffected by decreased maternal hemoglobin, which suggests that liability to schizophrenia renders cases susceptible to the deleterious influences of in utero exposure to decreases in maternal hemoglobin.

1. Introduction

Neuromotor disruptions have been consistently associated with schizophrenia, with such difficulties occurring premorbidly (as early as infancy) and in neuroleptic naïve patients (Walker et al., 1994; Wolff and O'Driscoll, 1999; Pappa and Dazzan, 2009). In addition, cognitive difficulties have been repeatedly deemed to be a core characteristic of schizophrenia (Kuperberg and Heckers, 2000). Although there is variability among studies, the most commonly replicated cognitive deficits among schizophrenia patients have been in the areas of attention, information processing, working memory, executive functioning, language and memory (Kuperberg and Heckers, 2000; Barch, 2005). Further, cognitive and motor problems have been found in children prior to the onset of schizophrenia, suggesting that these difficulties may have developmental origins and are not entirely the result of the confounding influences of medication use and symptom onset (Rosso et al., 2000; Reichenberg et al., 2006). Nevertheless, it is unclear whether motor and cognitive problems associated with schizophrenia are related to genetic vulnerability for schizophrenia, environmental factors, or a combination of genetic and environmental influences.

Despite a presumed large genetic component to the causes of schizophrenia, concordance rates approximating 50% between monozygotic twins indicate the presence of a substantial environmental influence in the etiology of the disorder (Cannon et al., 1998). Among the

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potential environmental contributors, pre- and perinatal complications have been among the most well-documented risk factors associated with schizophrenia (Cannon et al., 2002). Although many obstetric events have been examined in schizophrenia research, in a previous investigation derived from the birth cohort of the current study, decreases in maternal mean hemoglobin (Hb) levels during pregnancy were linked to a significant increase in risk for schizophrenia in a dose–response fashion (Insel et al., 2008). Further, maternal anemia during pregnancy has been associated with obstetric complications (OCs) that have been linked to schizophrenia, such as fetal hypoxia, maternal malnutrition during pregnancy, and low birth weight (Viteri, 1994; Rasmussen, 2001; Cannon et al., 2002; Casanueva and Viteri, 2003). Despite these findings, no study has investigated whether fetal exposure to low maternal Hb during pregnancy is related to motor and cognitive difficulties among patients with schizophrenia.

The present study sought to determine whether fetal exposure to decreases in maternal Hb was related to diminished neuromotor and neurocognitive performance among cases with schizophrenia and other schizophrenia spectrum disorders (herein referred to as schizophrenia) and matched controls. Based on repeated findings in animal studies linking fetal exposure to maternal anemia to neuromotor problems, as well as learning and memory difficulties, we predicted that fetal exposure to decreases in maternal Hb would be related to poorer performance on motor tasks, as well as learning and memory tasks in adulthood (Jorgenson et al., 2003; Beard et al., 2006; Lozoff and Georgieff, 2006; Lozoff et al., 2006). For this purpose, we conducted analyses of hemoglobin and neuromotor/neurocognitive performance separately in cases and controls. Further, it was hypothesized that cases, compared to controls, would be preferentially sensitive to decreases in maternal Hb with regard to function on these tests, consistent with previous studies examining the influences of hypoxia-associated OCs in schizophrenia populations (van Erp et al., 2002; Cannon et al., 2008). Hence, we also examined whether there was an interaction between case/control status and Hb in relation to neuromotor/neurocognitive performance. These latter analyses were considered to be exploratory associations, due to reduced power for testing interactions. Exploratory analyses also were conducted on measures of attention, working memory, and executive functioning due to the relationship between these cognitive domains and schizophrenia (Kuperberg and Heckers, 2000; Barch, 2005).

2. Materials and methods

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

2.1. Description of the cohort

The subjects were derived from the Developmental Insult and Brain Anomaly in Schizophrenia (DIBS) study, which was based on participants from the Prenatal Determinants of Schizophrenia (PDS) study. The PDS study was a follow-up of a large birth cohort to determine who among the offspring developed schizophrenia, described in detail in a previous publication (Susser et al., 2000). Briefly, the PDS study included pregnant women (N = 12,094 live births) receiving obstetric care from the Kaiser Permanente Medical Care Plan (KPMCP) in Alameda County, California, as part of the Child Health and Development Study (CHDS). Maternal Hb data were available for 6872 of 7791 mothers of the PDS Cohort (88.2%), which were extracted from detailed prenatal medical records.

2.2. Ascertainment and diagnosis

The protocol for ascertainment and diagnosis of schizophrenia cases is described in detail in a previous publication (Susser et al., 2000). Computerized record linkage between the CHDS and KPMCP identifiers from inpatient, outpatient, and pharmacy registries was conducted to ascertain schizophrenia cases from the CHDS cohort. Ascertained cases consisted of cohort members who belonged to KPMCP from 1981 to 1997. Potential cases were diagnosed by DSM-IV criteria following assessment with the Diagnostic Interview for Genetic Studies (DIGS) (Nurnberger et al., 1994), chart review, and consensus of 3 experienced research psychiatrists based on the DIGS and psychiatric/medical records. Comparison subjects were matched 1:1 to the case subjects on membership in KPMCP at the time of case ascertainment, date of birth, sex, and availability of maternal sera (reviewed in Brown et al., 2009).

All cases were targeted for neuropsychological assessment. Twenty-six cases and 24 controls completed neuropsychological assessments and of these participants, 24 cases and 22 controls had available mean Hb data from their mothers' pregnancies. As Table 1 indicates, there were no significant differences between cases and controls on a variety of demographic characteristics.

2.3. Hemoglobin assessment

Hb is a protein found in red blood cells, which carries oxygen from the lungs to peripheral tissues and is decreased with anemia (Bunn and Poyton, 1996). Hb is an excellent indicator of iron status and blood oxygenation (Bunn and Poyton, 1996; Tam and Lao, 1999). Maternal Hb concentrations from blood samples collected throughout pregnancy were extracted from obstetric records. Hb values were available from 14 subjects (7 cases) in the first trimester, from 34 subjects (18 cases) in the second trimester, and from all subjects in the third trimester. To maximize power, and in accord with the previous association between mean prenatal Hb levels and risk for schizophrenia, mean Hb levels throughout pregnancy were used in the present study (Insel et al., 2008). The majority of subjects (17

Table 1
Demographic characteristics of the samples (Means, standard deviations, frequencies, and percentages).

Characteristic	Schizophrenia cases (n = 24)	Control subjects (n = 22)	p-Value
Female offspring	25.00%	31.82%	0.608
Age of offspring at testing	39.77 (1.83)	40.87 (1.91)	0.052
Birth weight (grams)	3451.61 (611.44)	3246.08 (569.74)	0.246
Gestational age (weeks)	40.66 (1.89)	39.78(1.59)	0.103
Maternal age	28.29(6.52)	28.23 (5.85)	0.972
# of previous deliveries	2.00 (2.14)	1.27 (1.28)	0.172
Maternal education			
(≥HS grad)	65.22%	54.55%	0.465
Maternal race			
Caucasian	12 (50%)	12 (54.55%)	0.725
African American	10 (41.67%)	7 (31.82%)	
Other	2 (8.33%)	3 (13.64%)	
Hemoglobin (g/dL)	10.871 (0.84)	11.327 (1.20)	0.138
Medication use			
Atypical antipsychotics[a]	8 (33.33%)	0	0.003
Typical antipsychotics	5 (20.83%)	0	0.023
Any antipsychotic	10 (41.67%)	0	0.0006
Anti-pyramidal medications	5 (20.83%)	0	0.023
Mood stabilizers	6 (25.00%)	0	0.012
SSRIs	3 (12.50%)	0	0.086
Ritalin	1 (4.17%)	0	0.333
Vicodin	0	1 (4.55%)	0.291
Benzodiazepines	1 (4.17%)	0	0.333

HS = high school; g/dL = grams per deciliter.
[a] 1 subject was taking Clozaril.

controls/19 cases; 80%) had at least 2 available Hb values from different trimesters.

2.4. Neuropsychological assessment

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 primary neuropsychological measures were chosen to assess motor, memory, and overall cognitive abilities. Neuromotor tasks used in the present study were Finger Tapping and Grooved Pegboard (Lezak et al., 2004). These tasks were chosen due to observed motor disturbances in schizophrenia and due to associations between maternal anemia during pregnancy and motor disturbances in offspring (Beard et al., 2006; Lozoff and Georgieff, 2006; Lozoff et al., 2006). IQ was calculated using Kaufman's triad, which is an IQ estimate using 3 subscales of the Wechsler Adult Intelligence Scale — Third Edition (WAIS-III), picture completion, digit span, and information (Kaufman, 1990; Boone, 1992; Lezak et al., 2004). This estimate has very good reliability and predictive validity and has been validated in multiple populations, including psychiatric inpatient populations (Boone, 1992; Lezak et al., 2004).

The California Verbal Learning Test — Version II (CVLT-II) was used to assess learning and memory. Short and long-delay recall scores were used, because these domains appear to be most affected in schizophrenia and have been associated with maternal anemia during pregnancy in offspring (Jorgenson et al., 2003; van Erp et al., 2008).

For exploratory purposes, short-term and working memory, and executive function measures were examined. Short-term and working memory tasks included the WAIS-III subscales digit span and letter–number sequencing (Lezak et al., 2004). The executive function tasks, the Modified Wisconsin Card Sorting Test (MWCST) and Trails B tests, were chosen based on previous studies of relationships between OCs and performance on these measures (e.g. Yurgelun-Todd and Kinney, 1993; Brown et al., 2009). Trails A times were subtracted from Trails B times in order to assess executive function, while adjusting for processing speed and sequencing (Lezak et al., 2004). Standardized scores (scaled scores, z-scores, and T-scores) were used for the CVLT-II and the WAIS-III measures based on published norms given that these measures utilized very large norming populations, whereas raw scores were used for the remaining measures due to small and potentially biased available norming populations (e.g. Ruff and Parker, 1993).

2.5. Statistical analyses

All analyses were conducted in SAS version 9.1 (SAS, Inc., Cary, N.C.). Neuropsychological scores were examined to determine normality by visually examining these data and examining kurtosis and skewness values. Dependent measures with non-normal distributions were log-transformed. ANOVAs were conducted to provide descriptive statistics and to replicate previous case/control differences in neuropsychological measures. Multiple regressions were conducted separately in cases and controls to determine whether maternal mean Hb values during pregnancy were significantly related to neuromotor and neuropsychological performance. Multiple regressions then were conducted with Hb by case status interaction terms to determine whether there may be preferential sensitivity to lower Hb in utero among cases compared to controls. Due to power considerations, the interaction models were viewed as tentative. Maternal education at birth (high school graduate or below vs. higher education), a robust indicator of socioeconomic status, was controlled for in analyses as a proxy variable for postnatal adversity to account for the potential contributions of postnatal disadvantages to neuropsychological performance. In studies examining prenatal contributors to adult outcomes, variables like maternal education at birth are frequently controlled for due to the high likelihood that the postnatal environment influences adult functioning, even though such variables may not always be related to case/control differences (Schlotz and Phillips, 2009).

There were no significant differences in other demographic characteristics between cases and controls; therefore we did not control for these variables (see Table 1). While there were significant differences in medication use between cases and controls (see Table 1), there were no significant differences in maternal Hb values during pregnancy among offspring who were on medication compared to offspring on no medication ($F = 0.65$, $df = 1$, $p = 0.424$) or offspring on antipsychotics compared to offspring on no antipsychotics ($F = 0.42$, $df = 1$, $p = 0.521$); therefore we did not control for medication use. Statistical significance was based on $p < 0.05$; all tests were two-tailed.

3. Results

Based on evaluation of skewness, kurtosis, and visual inspection of the dependent variables, Grooved Pegboard dominant time (skewness = 3.23, kurtosis = 13.07), Trails B–Trails A times (skewness = 2.92, kurtosis = 10.80), and MWCST total errors (skewness = 1.31, kurtosis = 0.86) all had non-normal distributions; therefore these data were log-transformed. As expected, cases performed significantly worse than controls on all of the measures (see Table 2).

As Table 3 indicates, among cases, as maternal Hb during pregnancy decreased there were significant decreases in performance on all of the motor tasks and the WAIS-III information subtest, after controlling for maternal education. Secondary analyses indicated that decreases in maternal Hb were associated with non-significant decreases in

Table 2
ANOVA results of differences in neuropsychological performance between cases and controls.

Neuropsychological measures	Cases	Controls	F-value	p-value
	Mean (SD)	Mean (SD)		
General intellectual functioning				
Full scale IQ estimate[a]	92.833 (14.826)	108.227 (14.396)	12.722	0.001
WAIS info total SS	15.600 (5.595)	19.318 (5.489)	4.719	0.036
Picture completion SS	16.600 (4.547)	20.636 (4.573)	8.210	0.007
Motor functioning				
Grooved Pegboard: dominant times	100.458 (45.749)	68.636 (7.950)	15.806	<0.0001
Grooved Pegboard: non-dominant times	100.792 (23.583)	72.727 (9.062)	27.402	<0.0001
Finger Tapping: # of total taps	84.8333 (33.717)	115.000 (22.991)	11.936	0.001
Learning and memory				
CVLT short delay free recall z-scores	−1.0833 (1.186)	0.0714 (1.052)	11.789	0.001
CVLT long delay free recall z-scores	−1.375 (1.270)	−0.3095 (1.219)	8.177	0.007
Short-term and working memory				
WAIS digit span SS[a]	8.7916 (2.637)	10.4545 (2.686)	4.484	0.040
Letter–number SS	7.5416 (2.963)	10.1363 (3.137)	8.323	0.006
Executive functioning				
Trails B–Trails A times	63.286 (46.412)	28.773 (9.325)	13.680	0.0006
MWCST errors	15.792 (11.718)	6.727 (5.88)	9.299	0.004

Means and SDs based on raw and standardized scores are presented in Table 2 for descriptive purposes; however, F and p-values for analyses using Trails B–Trails A times, grooved pegboard dominant and MWCST total errors were based on the log-transformed scores. SS = scaled scores.

[a] WAIS digit span also was one of the subtests comprising the full scale IQ estimates.

Table 3
Results of unadjusted and adjusted regression analyses of maternal Hb and neuropsychological performance.

Measure	Cases, unadjusted			Cases, adjusted for maternal education			Controls, unadjusted			Controls, adjusted for maternal education		
	Parameter estimate	95% CI	p-value	Parameter estimate	95% CI	p-value	Parameter estimate	95% CI	p-value	Parameter estimate	95% CI	p-value
Primary measures												
General intellectual functioning												
Full scale IQ estimate[a]	7.041	−0.158, 14.241	0.055	6.763	−0.360, 13.887	0.062	4.397	−0.832, 9.627	0.095	3.951	−1.134, 9.035	0.120
WAIS information SS	2.118	0.648, 3.588	0.007	1.924	.681, 3.166	0.005	0.961	−0.179, 2.100	0.0939	0.909	−0.025, 3.794	0.118
Picture completion SS	1.072	−1.588, 3.731	0.408	1.044	−1.718, 3.807	0.436	0.450	−1.322, 2.222	0.602	0.387	−1.430, 2.204	0.661
Motor functioning												
Grooved Pegboard dominant (log)	−0.185	−0.355, −0.016	0.034	−0.197	−0.351, −0.043	0.015	−0.004	−0.049, 0.041	0.860	0	−0.045, 0.044	0.986
Grooved Pegboard non-dominant	−15.414	−25.866, −4.962	0.006	−15.949	−25.009, −6.889	0.002	−0.182	−3.717, 3.353	0.916	−0.091	−3.734, 3.552	0.959
Finger Tapping	19.055	3.330, 34.779	0.020	18.75	3.490, 34.010	0.019	−4.834	−13.549, 3.882	0.260	−0.223	−1.470, 1.023	0.712
Learning and memory												
CVLT short delay z-scores	−0.229	−0.848, 0.390	0.451	−0.225	−0.871, 0.421	0.476	0.235	−0.163, 0.632	0.232	0.188	−0.186, 0.562	0.304
CVLT long delay z-scores	2.541	−0.657, 0.687	0.963	0.033	−0.624, 0.691	0.917	0.517	0.108, 0.927	0.016	0.446	0.118, 0.774	0.01
Secondary measures												
Short-term and working memory												
WAIS digit span SS[a]	0.661	−0.703, 2.026	0.326	0.680	−0.755, 2.114	0.335	0.759	−0.227, 1.745	0.124	0.674	−0.284, 1.633	0.157
Letter–number SS	1.205	−0.269, 2.680	0.104	1.260	−0.223, 2.742	0.092	0.223	−0.180, 0.625	0.262	0.629	−0.577, 1.835	0.289
Executive functioning												
Trails B–Trails A times (log)	−0.154	−0.564, 0.256	0.441	−0.148	−0.586, 0.290	0.485	−0.102	−0.225, 0.021	0.100	−0.091	−0.210, 0.028	0.127
MWCST errors (log)	−0.142	−0.608, 0.324	0.534	−0.157	−0.643, 0.329	0.508	−0.095	−0.421, 0.230	0.546	−0.093	−0.431, 0.244	0.568

[a] WAIS digit span also was one of the subtests comprising the full scale IQ estimates.

performance on IQ and letter–number sequencing, controlling for maternal education (see Table 3). Among controls, decreases in maternal Hb were significantly related to diminished performance on CVLT long-delay recall, after controlling for maternal education (see Table 3). Further, there were significant case status by Hb interactions for all of the motor tasks, such that fetal exposure to decreases in Hb during pregnancy were associated with poorer motor performance among cases, but not controls (see Table 4 for all interaction results and Fig. 1 for significant interactions). No significant case status by Hb interactions were found for any of the other measures.

4. Discussion

The present study is the first to examine maternal Hb during pregnancy in relation to long-term neuromotor and neuropsychological functioning in schizophrenia. As has been found in previous studies, schizophrenia cases showed significantly poorer performance on all of the neuromotor and neuropsychological measures used in the present study compared to controls; however, lower maternal Hb during pregnancy was associated with further, statistically significant decreases in performance on the motor tasks and the WAIS-III information subtest among cases (e.g. Kuperberg and Heckers, 2000). Further, the present study indicated that cases may be preferentially sensitive to decreases in maternal Hb during pregnancy, with more neuromotor difficulties compared to controls, suggesting that liability for the disorder may render fetuses vulnerable to lower maternal Hb. Neuromotor dysfunction has been isolated as a core deficit in schizophrenia, with disturbances occurring premorbidly (as early as infancy) and persisting throughout the course of the disorder (Walker et al., 1994; Wolff and O'Driscoll, 1999; Mittal and Walker, 2007; Pappa and Dazzan, 2009). Fine motor problems, motor coordination difficulties, and unusual movements have all been observed in the premorbid periods of schizophrenia and after symptom onset (Walker et al., 1994; Wolff and O'Driscoll, 1999; Rosso et al., 2000; Mittal and Walker, 2007; Pappa and Dazzan, 2009). Further, previous findings suggest that fetal hypoxia is related to premorbid motor abnormalities among children who later develop schizophrenia in adulthood (Rosso et al., 2000). This finding is especially relevant to the present study, as anemia during pregnancy has been associated with fetal hypoxia, suggesting that some of the premorbid motor difficulties found in schizophrenia may be partially attributable to decreases in maternal Hb during pregnancy (Bunn and Poyton, 1996).

In rodents, pre- and perinatal iron deficiency have been linked to a range of alterations in basal ganglia functioning (e.g. increased dopamine) and correlated disruptions in motor behavior among offspring (Weinberg et al., 1980; Beard et al., 2006; Lozoff and Georgieff, 2006). Further, these disruptions do not seem to be ameliorated by iron supplementation after weaning (Felt et al., 2006). These findings are particularly relevant to schizophrenia, as basal ganglia dysfunction, such as increases in dopamine, have been repeatedly linked to schizophrenia populations and have been noted in the prodrome of the disorder, suggesting a possible neurodevelopmental origin to this brain pathology (Abi-Dargham, 2005; Howes et al., 2009). Lastly, fetal exposure to maternal anemia has been associated with decreased myelination in rodent offspring, which

Table 4
Results of regression analyses of the relationship between maternal Hb by case status on neuropsychological performance.

Measure	Interactions terms for case status by Hb Unadjusted			Interaction terms for case status by Hb Adjusted for maternal education		
	Parameter estimate	95% CI	p-Value	Parameter estimate	95% CI	p-Value
Primary measures						
General intellectual functioning						
Full scale IQ estimate	2.644	−5.984, 11.271	0.540	9.158	−135.603, 48.350	0.498
WAIS information SS	1.157	−0.709, 3.023	0.217	1.124	−0.647, 2.896	0.207
Picture completion SS	0.622	−2.475, 3.719	0.687	0.607	−2.520, 3.733	0.697
Motor functioning						
Grooved Pegboard dominant log	−0.182	−0.338, −0.025	0.024	−0.201	−0.343, −0.059	0.007
Grooved Pegboard non-dominant	−15.232	−25.190, −5.273	0.004	−16.340	−25.488, −7.190	0.0008
Finger Tapping	23.889	6.943, 40.835	0.007	24.308	7.476, 41.140	0.006
Learning and memory						
CVLT short delay z-score	−0.464	−1.168, 0.240	0.190	−0.427	−1.123, 0.268	0.222
CVLT long delay z-score	−0.502	−1.251, 0.247	0.183	−0.426	−1.101, 0.249	0.209
Secondary measures						
Short-term/working memory						
WAIS digit span SS[a]	−0.098	−1.729, 1.534	0.904	−0.030	−1.668, 1.608	0.970
Letter–number SS	0.525	−1.330, 2.381	0.571	0.637	−1.212, 2.486	0.490
Executive functioning						
Trails B–Trails A times log	−0.053	−0.419, 0.314	0.773	−0.062	−0.435, 0.311	0.739
MWCST errors log	−0.047	−0.594, 0.501	0.865	−0.059	−0.619, 0.501	0.832

[a] WAIS digit span also was one of the subtests comprising the full scale IQ estimates.

may contribute to our findings, given that all of the neuromotor tasks involved a speeded component (Yu et al., 1986).

The present study also found that decreases in maternal Hb during pregnancy were associated with significantly diminished function on the WAIS information subtest (a measure of overall general knowledge) and diminished IQ, which approached significance, in cases. For the latter finding, the magnitude of association was large, such that each unit decrease in maternal Hb was associated with a 7-point decrease in IQ scores. These results are consistent with observed decreases in IQ among children prior to the onset of

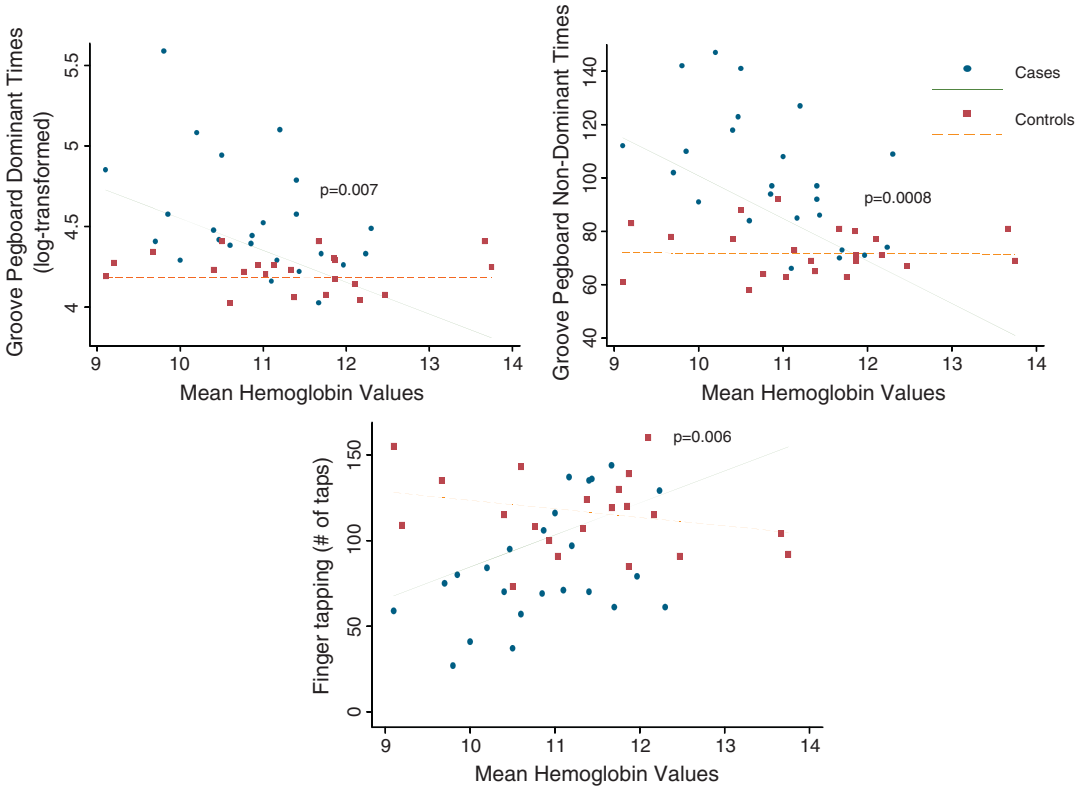

Fig. 1. Relationship between hemoglobin levels, case status, and motor performance. Figure 1 displays the raw mean hemoglobin levels for cases and controls by scores on the motor tasks Grooved Pegboard and Finger Tapping. Each graph includes separate regression lines for cases and controls controlling for maternal education (maternal education was held constant as above high school education). The graphs display p-values for the interaction terms from regression models testing whether case status interacts with hemoglobin levels to influence motor performance, also controlling for maternal education. Longer times on Grooved Pegboard indicate poorer performance, whereas increased number of taps on Finger Tapping indicate better performance.

psychosis and decreases in premorbid WISC information scores following fetal exposure to influenza, suggesting that prenatal factors may contribute to these premorbid cognitive problems (Reichenberg et al., 2006; Ellman et al., 2009).

Contrary to our hypothesis, cases exhibited no significant decreases in performance on learning and memory tasks after fetal exposure to lower Hb, although decreases in maternal Hb were associated with decreased performance on long-delay recall among controls. Nevertheless, similar findings were not observed on short-delay scores and there was no case status by Hb interaction for any CVLT measures. Given the potential for Type 1 error, it is difficult to interpret these findings. Future studies with larger samples are needed to determine whether exposure to lower maternal Hb during pregnancy is related to decrements on hippocampal-dependent tasks.

Maternal anemia during pregnancy has been associated with multiple OCs that have been implicated in schizophrenia, such as fetal hypoxia, malnutrition, and fetal growth restriction (Bunn and Poyton, 1996; Susser et al., 1996; Rasmussen, 2001; Cannon et al., 2002). It remains unclear whether the relationship between low maternal Hb during pregnancy and neuromotor/cognitive changes among schizophrenia patients is the direct consequence of anemia or rather multiple teratogenic contributors. Future studies are necessary to determine whether the results in the present study are solely due to decreases in maternal Hb during pregnancy or whether there may be multiple OCs operating in conjunction with each other to disrupt fetal neural development. In addition to comprehensive and prospectively collected data on OCs, studies would require larger sample sizes than in the present study to explore interactive and mediating effects.

4.1. Limitations

Given the multiple tests conducted in this study, it is possible that some of the findings of the secondary analyses may have arisen from Type I error. However, for the primary analyses the results were consistent across 3 neuromotor tasks, which reduce the probability of spurious findings. Second, the sample was limited to approximately 25% of cases from the overall cohort, raising the potential for selection bias. However, as reported previously, cases who participated in the DIBS study and cases from the original cohort who were not DIBS subjects did not differ with regard to several demographic variables; therefore, it is unlikely that case ascertainment bias accounts for our findings (Ellman et al., 2010). Bias would also be mitigated by the fact that the sample was derived from a population-based study, in contrast to other neuropsychological studies, which draw upon hospital or clinic-based samples.

Third, some of the null results may have been explained by Type II error due to the modest sample sizes. Hence, it is possible that use of a larger sample might have revealed significant associations between low maternal Hb and other neurocognitive functions in cases, as well as neuromotor and cognitive difficulties among controls.

Fourth, there is always the possibility that medication use among the schizophrenia cases in the present study influenced performance on neurocognitive tasks (Hill et al., 2010). Despite this possibility, there were no differences in Hb values between participants on antipsychotics versus those not on antipsychotics; therefore reducing the possibility that medication use confounded our results. Nevertheless, future studies would benefit from examining the relation between maternal Hb during pregnancy and cognition in premorbid and prodromal periods, which would reduce the likelihood of medication use influencing results.

In conclusion, the present study is the first to suggest that neuromotor and neurocognitive disturbances previously associated with schizophrenia may be partially attributable to fetal exposure to maternal anemia. Further, the neuromotor disturbances were limited to schizophrenia cases, suggesting potential gene–environment and/or environment–environment interactions that should be tested in future studies. Given that the prevalence of anemia among women in the United States is 9–11% and is believed to increase substantially during pregnancy, our findings have potential implications for efforts to develop primary prevention, early intervention, and treatment strategies for pregnant women to adhere to widely accepted recommendations of iron supplementation during pregnancy (Scholl, 2005).

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Contributors

Dr. Ellman conducted all of the statistical analyses, contributed substantially to the conceptualization of the paper, study design, data interpretation, and was the main writer of the manuscript. Dr. Deicken was a co-investigator of the study and contributed to theoretical understanding of neurobiological contributors to the findings. Drs. Vinogradov, Kremen, and Poole contributed to the conceptual design, to data collection, data interpretation, and manuscript writing. Mr. Kern aided in data management and consultation pertaining to statistical analyses, interpretation of the data, and contributed to manuscript writing. Dr. Brown contributed to all areas pertaining to study conceptualization, study design, participant ascertainment, interpretation of the findings, and manuscript writing.

Conflict of interest

The authors have no financial disclosures and/or conflicts to report.

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