Published in final edited form as:
Prog Neuropsychopharmacol Biol Psychiatry. 2011 August 1; 35(6): 1525–1529. doi:10.1016/j.pnpbp.2011.04.012.

Maternal-fetal Blood Incompatibility and Neuromorphologic Anomalies in Schizophrenia: Preliminary Findings

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Abstract

Prior research has shown that maternal-fetal Rhesus (Rh) and ABO blood incompatibility increase the risk for schizophrenia. In the present study, the relationship between blood incompatibility and volumes of brain structures previously implicated in schizophrenia was assessed in schizophrenia cases and controls from a large birth cohort. Rh/ABO incompatible cases had significantly reduced cortical gray matter volume compared to compatible cases, a finding which appears to be driven by significant volume reductions in the dorsolateral prefrontal cortex and inferior frontal cortex. Larger hippocampal and putamen volumes were also observed in exposed controls compared to unexposed controls. Although the sample size is small and replications are required, these data suggest that maternal/fetal blood incompatibility may increase the risk for altered brain morphology in both schizophrenia and in controls. The findings also suggest that the larger hippocampal volume in exposed controls may indicate a mechanism of adaptive resilience which diminishes the risk that controls will develop schizophrenia.

Keywords

schizophrenia; neuroimaging; dorsolateral prefrontal cortex- blood incompatibility; hippocampus; brain morphology

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Research highlights: This study suggests two main, preliminary conclusions. First, in utero exposure to blood incompatibility is related to risk for structural brain changes which in turn are associated with risk of developing schizophrenia. Second, exposed controls had significantly larger hippocampi than unexposed controls, a finding that was not observed in the cases. One possible explanation for this finding, though speculative, is that the exposed controls' enlarged hippocampus may be protective against the development of disease by an adaptive resilience.

Prior research has shown that maternal-fetal blood incompatibility heightens the risk for schizophrenia later in life. In the pioneering study, Hollister et al (1996) found that second and later born offspring of Rhesus (Rh) incompatible pregnancies had an increased occurrence of schizophrenia (Hollister, Laing et al. 1996). More recently, from the birth cohort of the present study, Insel et al (2005) found that both Rh and ABO incompatibility increased the risk of schizophrenia in second and later born offspring, with greater risk for males than females (Insel, Brown et al. 2005). These findings have been observed by others, including in three meta-analyses (Geddes and Lawrie 1995; Cannon, Jones et al. 2002; Palmer, Mallery et al. 2008; Palmer 2010).

Rh incompatibility occurs when an Rh negative mother becomes pregnant with an Rh positive fetus. Maternal alloantibodies in response to Rh D antigen cross the placenta, causing hemolytic disease, leading to hyperbilirubinemia in the fetus and newborn and subsequent brain damage (Hollister, Laing et al. 1996). At the extreme, kernicterus results. Infants who survive kernicterus typically manifest signs of overt brain dysfunction including mental retardation or other cognitive impairments, motor dysfunction and hearing deficits (Watchko and Oski 1992; Creasy, Resnik et al. 2004). Hollister et al (1996) proposed that Rh incompatibility may be related to schizophrenia based in part on the common central nervous system (CNS) sequelae: neuromotor and neurocognitive dysfunction. ABO incompatibility also causes hemolytic disease of the newborn and has similar potential effects on brain development. As a result of successful prophylactic treatments for Rh incompatibility, mainly in the developed world, ABO incompatibility may be a more significant cause of hemolytic disease among offspring in these countries (Murray and Roberts 2007).

First episode and prodromal studies of patients with schizophrenia have documented differences in brain structure for those who later develop schizophrenia or psychosis, suggesting that these neuromorphologic influences are present before onset of the disorder (Pantelis, Velakoulis et al. 2003; Seidman, Giuliano et al. 2010). Documenting associations between known risk factors for schizophrenia, such as Rh incompatibility, could help identify risk factors for structural brain changes in schizophrenia, and validate their potential role in the etiology of this disorder (Brown 2011).

In the Developmental Insult and Brain Anomaly (DIBS) study, volumetric neuroanatomy was assessed in adulthood among schizophrenia cases and matched controls from the Child Health and Development Study (CHDS) birth cohort. In previous studies from the DIBS, prenatal infection was related to increased size of the cavum septum pellucidum (Brown, Deicken et al. 2009) and maternal elevations in the cytokine maternal interleukin-8 was associated with increased cerebrospinal fluid (CSF) ventricular volume (Ellman, Deicken et al. 2010). In this preliminary study, we assessed the relationship between Rh and ABO blood incompatibility and neuromorphologic alterations in the DIBS sample. For this purpose, we conducted stratified analyses consisting of within-group (case, control) comparisons of volumetric brain outcomes between subjects exposed and unexposed to blood incompatibility. Since there have been many previous and much larger studies that have documented regional brain volume differences between schizophrenia cases and controls (Nelson, Saykin et al. 1998; Shenton, Dickey et al. 2001; Steen, Mull et al. 2006), we did not aim to replicate those well established findings.

Method

The cases and controls in the DIBS were drawn from a schizophrenia follow-up investigation of the Child and Health Development Study (CHDS), a birth cohort of 19,044 live births in Northern California at Kaiser Permanente Hospitals born between 1959 and

1967 (Susser, Schaefer et al. 2000; Brown, Vinogradov et al. 2009). Cases were ascertained by computerized record linkage from identifiers in the CHDS and Kaiser Permanente databases. Cases (N=71) were assessed with the Diagnostic Interview for Genetic Studies (Nurnberger, Blehar et al. 1994) for DSM-IV diagnosis based on consensus of three senior research psychiatrists. All cases and matched controls were targeted for neuroimaging assessments in adulthood. The DIBS sample consisted of all cases with complete neuroimaging assessments (N=26: 13 with schizophrenia, 7 with schizoaffective disorder and 6 with other schizophrenia spectrum disorders), and 25 controls matched on date of birth; sex, and availability of maternal serum samples. Cases in the DIBS were similar to subjects in the overall sample with regard to maternal age, race, education and parity (Brown, Vinogradov et al. 2009). At the time of imaging, case subjects were an average of 40 (SD = 1.8) years old and control subjects had an average age of 41.2 (SD = 1.7) years. Maternal self-report of race for case subjects included: 12 Whites, 5 African-American and 2 “Other”; maternal self-report of race for control subjects included 12 Whites, 6 African-Americans and 3 “Other”.

Maternal-fetal Rh and ABO incompatibility were assessed by analysis of blood samples in the CHDS birth cohort at the time of the blood draws (Insel, Brown et al. 2005). Exposure to maternal-fetal Rh incompatibility was defined as an Rh-negative (D antigen of Rh) gravida and an Rh-positive fetus. Exposure to maternal-fetal ABO incompatibility was defined as a gravida with blood type O and a fetus with blood type A or B. Given the small number of cases, these two definitions were combined into a composite exposure, representing either Rh incompatibility or ABO incompatibility (heretofore referred to as “composite Rh/ABO incompatibility”), in accord with a previous study in this birth cohort (Insel, Brown et al. 2005) (see Table 1). Complete data on both maternal-fetal composite blood incompatibility status and regional brain volumes were available on 19 cases (80.7 percent of those with SSD in the DIBS sample) and 21 controls (84% of controls in the DIBS).

Image acquisition and analysis

As described previously (Ellman, Deicken et al. 2010), MR images for this cohort were acquired using a 1.5-Tesla Siemens system. Coronal T1-weighted images were obtained from 3D MP-RAGE sequences (TR/TI/TE = 10/250/4 ms, resolution 1×1 mm^2, 1.4 mm slice thickness). MRI tissue segmentation and regional voluming in the Talairach coordinate system were used based on previously detailed methods (Collins, Zijdenbos et al. 1998; Kwan, Evans et al. 1999) which have been shown to be reliable (Manji, Moore et al. 2000) and valid (Fein, Di Sclafani et al. 2000). In-house software was used to: 1) remove the skull and meninges from the images; 2) co-register each of the interleaves of the spin-echo images to T1 images reformatted to the axial plane; 3) perform RF inhomogeneity correction in 3D; and 4) transfer the data to statistical software which performs the actual cluster analysis.

Next, computer-assisted segmentation of cortical and subcortical gray matter, white matter, and ventricular and sulcal CSF was conducted, followed by manual demarcation of the boundaries of cortical regions, subcortical structures, the cerebellum, and the hippocampi. The transformation to the Talairach coordinate system involved piecewise linear transformations of 12 compartments for each subject’s brain. Each subject’s tissue contribution to the commonly defined ROI was then computed by superimposing the subject-specific region of interest (ROI) on the subject’s segmented image, and counting the (segmented) pixels contained in the ROI.

The thalamus and hippocampus were manually traced as described previously (Ellman, Deicken et al. 2010). The head of the caudate was defined on the transaxial plane as the mass of gray matter comprising the lateral walls of the lateral ventricles bounded inferiorly and laterally by the anterior limb of the internal capsule and superiorly and laterally by the

external capsule. Region placement for the caudate and the putamen began inferiorly when the operator could see clearly at least on one side the anterior limb of the internal capsule dividing the caudate head and the putamen. The boundary for the head of the caudate continued superiorly until the thalamus could no longer be visualized and the anterior horn of the lateral ventricles became confluent with the posterior horn. The body of the caudate was defined as the portion above the thalamus after the confluence of the anterior and posterior horns of the lateral ventricles. The caudate tail was defined as a structure of gray matter closely adjacent anterolaterally to the posterior horns of the lateral ventricles and posterolaterally to the thalamus until it became confluent with the body of the caudate. The putamen is bounded laterally by the external capsule, and postero- and antero-medially by the internal capsule. The boundary between the putamen and the globus pallidus is noted by the difference between the two structures and when possible a strip of white matter was identified between the gray matter masses of the two structures. Regional tracing for the putamen extended superiorly until no more gray matter pixels could be detected medially to the claustrum band.

Reliability measures were performed on a mixture of the healthy reference population and study subjects of interest coded blindly to control for human operator bias and drawn from various times points throughout the study duration to control for instrumental (magnet) measurement deviation over time. For the semi-automated tissue segmentation and cortical voluming programs which required minimal human operator intervention, we routinely performed reliability measures on 20 brains. However, for brain structures that involved extensive human operator input to determine boundaries, reliability measures were scaled back to 10 brains after an initial comparison with 20 brains in earlier studies showed no significant differences. Reliability correlations were between 0.91 and 0.99 for all brain measures.

All ROIs were divided by intracranial volume to correct for head size. Ratios were chosen instead of controlling for intracranial volumes, in order to minimize loss of degrees of freedom given the modest sample size.

Analytic Methods

Analyses were performed with generalized linear models (GLM). GLM are a flexible parametric class of models suitable for small datasets which can capitalize on the specific distributional and variance structures in the response variables of the study. In the present study, a gamma regression model was used because we found unequal variance and have continuous positive brain volumetric outcomes.

Two sets of analyses were conducted: first, exposed cases were compared to unexposed cases on volumes of select brain regions; and second, exposed controls were compared to unexposed controls on the same regional brain volumes. In accord with the scope of the present study, volumetric brain outcomes were not compared between cases and controls.

Results

We first assessed whether there were significant relationships between blood incompatibility and potential confounding variables. No statistically significant differences were observed between the exposed and unexposed cases on age at time of neuroimaging ($p=0.36$), parity ($p=1.0$), infant sex ($p=1.0$), maternal age ($p=0.39$), maternal race ($p=1.0$), maternal education ($p = 1.0$), total duration of psychosis ($p=0.52$), or use of antipsychotic medication ($p=0.58$).

The composite Rh/ABO incompatible exposed cases, compared to unexposed cases, had significantly smaller total cortical gray matter volume (p=.016), as well as bilaterally diminished volumes of the dorsolateral prefrontal cortex (DLPFC; right, p = .002; left, p=. 024) and inferior frontal cortex (right, p = .044; left, p = .027)[See Table 2]. Consistent with these findings, a statistical trend was also observed for increased sulcal CSF volume in exposed cases (p=.07). In addition, there was a trend for diminished right thalamic volume in exposed cases (p=.09). In comparison, the ABO/Rh incompatible exposed controls, compared to unexposed controls, did not have smaller total cortical gray matter (p = .47) and had reductions in the DLPFC that were not statistically significant; but, similar to cases, had reduced bilateral volume in the inferior frontal cortex (right, p = .014; left, p = .016).

Exposed controls also had larger hippocampal volume than unexposed controls (total left hippocampus volume, p < .0001; total right hippocampus volume, p = .01) and enlarged right putamen volume (p = .016)[See Table 3]. Exposed controls also had reduced left occipital cortical volume (p = .08).

Discussion

We found preliminary evidence of significant volumetric differences between schizophrenia cases with and without maternal-fetal blood incompatibility, a putative risk factor for schizophrenia (Hollister, Laing et al. 1996; Palmer, Turunen et al. 2002; Insel, Brown et al. 2005; Palmer, Mallery et al. 2008; Palmer 2010), in total cortical gray matter, a finding which appeared to have been driven by diminished volumes of the dorsolateral prefrontal cortex (DLPFC) and the inferior frontal cortex. Smaller inferior cortical volume was observed in exposed controls, though there were no differences in total cortical volume including the DLPFC. These findings do not appear to have been confounded by several demographic variables, including maternal age, maternal education, maternal race, parity, infant sex, total duration of psychosis, subject age at time of neuroimaging assessment, or subject's current use of antipsychotic medication.

The findings lend themselves to two main conclusions. First, it is possible that in utero exposure to blood incompatibility heightens the risk for structural brain changes which in turn increase the risk of developing schizophrenia. Meta-analyses of brain volume differences in schizophrenia have previously reported diminished volume of the cortical brain regions associated with blood incompatibility in this study (Wright, Rabe-Hesketh et al. 2000; Steen, Mull et al. 2006); recent studies of cortical gray matter, including inferior cortical volumes in first episode psychosis and high risk subjects have found diminished volume of these brain regions prior to onset and after conversion into psychosis (Witthaus, Kaufmann et al. 2009; Buehlmann, Berger et al. 2010; Wood, Kennedy et al. 2010). In a randomized trial of cognitive enhancement therapy, Eack et al (2010), found that the treatment had a neuroprotective effect on gray matter volume, and improved neurocognitive functioning (Eack, Hogarty et al. 2010).

Second, exposed controls had significantly larger hippocampi than unexposed controls, a finding that was not observed in the cases. One possible explanation for this finding, though speculative, is that the exposed controls' enlarged hippocampus may be protective against the development of disease by an adaptive resilience. Hippocampal volume deficits have long been associated with schizophrenia and severity of psychotic symptoms (Bogerts, Lieberman et al. 1993; Chakos, Schobel et al. 2005; Steen, Mull et al. 2006; Pantelis, Velakoulis et al. 2007), although in some samples, non-reduction in hippocampal volume is associated with higher risk of psychosis (Phillips, Velakoulis et al. 2002). Moreover, the prefrontal cortex (PFC) and hippocampus have strong connectivity and hippocampal volume deficits probably manifest as deficits in executive function testing as a result (Bilder,

Bogerts et al. 1995). Furthermore, in animal studies, lesions in the ventral hippocampal region cause behavioral changes associated with the prefrontal cortex (Tseng, Lewis et al. 2008). Our results therefore suggest that the lack of conversion to psychosis following maternal/fetal blood incompatibility could involve stronger or more resilient PFC-hippocampal connectivity.

Most of what is known about the direct effects of Rh incompatibility derive from studies of infants and children who developed kernicterus, a condition characterized by severe CNS dysfunction secondary to bilirubin toxicity, though less severe outcomes, including mild mental retardation and subtle childhood neurocognitive deficits also have been described in Rh incompatible offspring (Odell, Schaffer et al. 1974; Rubin, Balow et al. 1979; Seidman 1991; Shapiro 2003; Chang, Lee et al. 2009). These outcomes are caused by increases in unconjugated bilirubin (UCB) triggered by lysis of fetal erythrocytes, as observed in hemolytic disease of the newborn. A number of brain regions have been implicated in CNS dysfunction secondary to hyperbilirubinemia, including the hippocampus, basal ganglia structures, and cerebellum (Shapiro 2003). Although the specific mechanisms remain to be fully elucidated, UCB reduces the viability of proliferating neurospheres, impairs neuronal differentiation (Fernandes, Falcao et al. 2009), and, at the molecular level, reduces NR1, NR2A, and NR2B subunits of NMDA receptors in the hippocampus, leading to disruptions in long term potentiation and depression (Chang, Lee et al. 2009), findings which have been implicated in schizophrenia (Lewis and Moghaddam 2006; Beneyto and Meador-Woodruff 2008; Henson, Roberts et al. 2008; Anastasio, Xia et al. 2009; Tamminga, Stan et al. 2010).

A strength of this study is that it draws on a well ascertained and longitudinally followed birth cohort from which maternal blood was drawn and tested shortly after birth, thereby reducing the possibility of bias. The primary limitation of this study is the small sample size, which may have reduced statistical power to demonstrate associations between blood incompatibility and neuromorphological changes in cases and controls, as well as limiting our ability to directly compare cases and controls as has been done in many larger case-control studies. A second limitation is the potential for false positive results due to multiple comparisons, which increases the likelihood of Type I error. Given the small sample, and the exploratory nature of the study, we elected not to control for multiple comparisons. Nevertheless, we have found significant relationships between maternal/fetal blood incompatibility and volumes in brain regions believed to be critical to the pathogenesis of schizophrenia, and these findings are more likely to have been underestimated rather than overestimated because one of the four exposed cases and two of the four exposed controls were first born, reducing the likelihood of complete development of maternal Rh alloantibodies (Hollister, Laing et al. 1996; Insel, Brown et al. 2005).

These preliminary findings may have implications for the prevention of brain abnormalities that underlie schizophrenia. Prophylactic treatments to prevent consequences of Rh D incompatibility did not become available until after this birth cohort was recruited (Insel, Brown et al. 2005), and such treatments are not widely available in developing countries. ABO incompatibility is not routinely tested in pregnancy and there are no recommendations for prevention of potential consequences to offspring. Hence, if these findings are replicated, consideration may be given to addressing the consequences of this prenatal exposure on offspring development. Moreover, given the relative paucity of data on the mechanisms by which Rh and ABO incompatibility alter fetal brain development, further investigation of these mechanisms may be merited.

Acknowledgments

Preparation of this manuscript was supported in part by NIMH Grant 1RO1MH-60249 (ASB), NIMH Grant 1KO2-MH65422 (ASB); NIMH Training Grant 5-T32-MH-13043 (DF); and Lieber Center for Schizophrenia Research (LSK).

Abbreviations used in the text

Rh	Rhesus
CNS	central nervous system
DIBS	Developmental Insult and Brain Anomaly
CHDS	Child Health and Development Study
CSF	cerebrospinal fluid
SSD	schizophrenia spectrum disorders
ROI	region of interest
DLPFC	dorsolateral prefrontal cortex
GLM	generalized linear models
PFC	prefrontal cortex (PFC)
UCB	unconjugated bilirubin

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Table 1

Rh/ABO Blood incompatibility exposure status among Schizophrenia Spectrum Disorder cases and controls in DIBS sample

Blood Incompatibility sample	Total sample size	Unexposed offspring		Exposed offspring	
		Control	Case	Control	Case
Rh Incompatibility	40	20	18	1	1
ABO Incompatibility	40	18	16	3	3
Composite Blood incompatibility	40	17	15	4	4

Table 2

Exposure to maternal-fetal composite Rh/ABO incompatibility and regional volumetric brain outcomes in subjects with schizophrenia or other schizophrenia spectrum disorder

Brain region/structure	Volume (cm^3)				P-value from Gamma model[A]
	Exposed case subjects (n=4)		Unexposed case subjects (n=15)		
	Mean	SD	Mean	SD	
Cortical Gray Matter	632.54	59.65	657.45	72.43	.0164
Dorsolateral Prefrontal Cortex Left	11.87	1.38	13.87	2.14	.0235
Dorsolateral Prefrontal Cortex Right	12.07	1.84	14.50	1.61	.0017
Orbitofrontal Cortex Left	22.04	3.83	20.57	4.29	.6132
Orbitofrontal Cortex Right	20.84	3.58	21.21	3.35	.5677
Inferior Frontal Cortex Left	9.98	1.32	11.25	1.65	.0266
Inferior Frontal Cortex Right	10.26	1.73	11.32	1.32	.0436
Superior Temporal Gyrus Left	13.27	2.16	13.97	1.41	.1214
Superior Temporal Gyrus Right	13.47	1.87	14.07	1.81	.2084
Ventricular CSF	33.98	16.42	31.11	12.86	.8204
Sulcal CSF	207.86	72.84	164.25	40.35	.0739
Subcortical Gray Matter	4.19	1.64	3.61	1.70	.5577
Total Hippocampus Left[B]	3295.08	441.15	3376.31	385.51	.6951
Total Hippocampus Right[B]	3772.96	420.89	3799.44	522.61	.9497
Caudate Left	4.87	0.27	5.09	0.56	.1534
Caudate Right	5.09	0.54	5.11	0.53	.5136
Putamen Left	5.21	0.58	5.54	0.74	.2124
Putamen Right	5.36	0.34	5.62	0.82	.3286
Thalamus Left	6.53	0.77	6.72	0.80	.3895
Thalamus Right	6.45	0.80	6.85	0.77	.0922
White Matter	589.01	33.93	571.74	71.92	.6161
Intracranial	1502.78	166.05	1463.26	172.71	.6688[C]

[A] Adjusted for intracranial volume (cm^3)

[B] Measured in mm^3

[C] P value without adjustment for intracranial volume

Prog Neuropsychopharmacol Biol Psychiatry. Author manuscript; available in PMC 2012 August 1.

Table 3

Exposure to maternal-fetal composite Rh/ABO incompatibility and regional volumetric brain outcomes in control subjects

Brain region/structure	Volume (cm^3)				P-value from Gamma model[A]
	Exposed control subjects (n=4)		Unexposed control subjects (n=17)		
	Mean	SD	Mean	SD	
Cortical Gray Matter	664.60	56.64	665.15	74.43	.4740
Dorsolateral Prefrontal Cortex Left	13.11	2.55	14.06	1.85	.1784
Dorsolateral Prefrontal Cortex Right	13.24	2.46	14.17	1.76	.1002
Orbitofrontal Cortex Left	19.27	4.23	20.83	4.03	.3671
Orbitofrontal Cortex Right	18.92	4.30	20.92	3.63	.1727
Inferior Frontal Cortex Left	10.31	1.47	11.47	1.45	.0162
Inferior Frontal Cortex Right	10.26	1.01	11.32	1.48	.0136
Superior Temporal Gyrus Left	13.48	1.61	14.06	1.91	.2468
Superior Temporal Gyrus Right	13.74	1.09	14.23	1.78	.1885
Ventricular CSF	29.06	7.75	27.07	8.91	.6603
Sulcal CSF	173.88	9.97	178.87	37.05	.6521
Subcortical Gray Matter	4.65	0.56	4.40	1.13	.6880
Total Hippocampus Left[B]	4354.26	649.91	3656.74	307.79	<.0001
Total Hippocampus Right[B]	4543.33	869.11	3948.63	359.42	.0105
Caudate Left	5.08	0.67	4.89	0.62	.5268
Caudate Right	5.25	0.74	5.03	0.71	.4214
Putamen Left	5.79	0.72	5.38	0.68	.1720
Putamen Right	5.80	0.52	5.26	0.71	.0163
Thalamus Left	6.93	0.88	6.47	0.65	.2075
Thalamus Right	6.78	0.78	6.39	0.56	.2033
White Matter	594.93	70.25	574.79	65.64	.5516
Intracranial	1502.92	119.98	1484.04	154.10	.8136[C]

[A] Adjusted for intracranial volume (cm^3)

[B] Measured in mm^3

[C] P value without adjustment for intracranial volume