Schizophrenia Research 121 (2010) 46–54

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

# Structural brain alterations in schizophrenia following fetal exposure to the inflammatory cytokine interleukin-8

Lauren M. Ellman [a,*], Raymond F. Deicken [b], Sophia Vinogradov [b,c], William S. Kremen [d], John H. Poole [e], David M. Kern [h], Wei Yann Tsai [f], Catherine A. Schaefer [g], Alan S. Brown [h,i]

[a] Department of Psychology, Temple University, Philadelphia, PA, United States
[b] Department of Psychiatry, University of California San Francisco, San Francisco, CA, United States
[c] Mental Health Service, San Francisco Department of Veteran Affairs Medical Center, San Francisco, CA, United States
[d] Department of Psychiatry, Center for Behavioral Genomics, University of California San Diego, and Center of Excellence for Stress and Mental Health, VA San Diego Healthcare System, La Jolla, CA, United States
[e] Department of Neuropsychology, Defense & Veterans Brain Injury Center, Veterans Affairs Health Care System, Palo Alto, CA, United States
[f] Department of Biostatistics, Mailman School of Public Health, Columbia University, United States
[g] Kaiser Permanente Division of Research, Oakland, CA, United States
[h] Department of Psychiatry, College of Physicians and Surgeons of Columbia University, New York State Psychiatric Institute, New York, NY, United States
[i] Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, NY, United States

ARTICLE INFO

*Article history:*
Received 27 October 2009
Received in revised form 11 May 2010
Accepted 12 May 2010
Available online 9 June 2010

*Keywords:*
Obstetric complications
Schizophrenia
Proinflammatory cytokines
Structural MRI
Pregnancy
Infection

ABSTRACT

*Background:* Maternal infection during pregnancy has been repeatedly associated with increased risk for schizophrenia. Nevertheless, most viruses do not cross the placenta; therefore, the damaging effects to the fetus appear to be related to maternal antiviral responses to infection (e.g. proinflammatory cytokines). Fetal exposure to the proinflammatory cytokine interleukin-8 (IL-8) has been significantly associated with risk of schizophrenia in offspring. This study sought to determine the association between fetal exposure to IL-8 and structural brain changes among schizophrenia cases and controls.
*Methods:* Subjects were 17 cases diagnosed with schizophrenia from the Developmental Insult and Brain Anomaly in Schizophrenia (DIBS) study. Psychiatric diagnoses were determined among offspring with semi-structured interviews and medical records review. IL-8 was determined from assays in archived prenatal sera and volumetric analyses of neuroanatomical regions were obtained from T1-weighted magnetic resonance imaging in adulthood. Eight controls were included for exploratory purposes.
*Results:* Among cases, fetal exposure to increases in IL-8 was associated with significant increases in ventricular cerebrospinal fluid, significant decreases in left entorhinal cortex volumes and significant decreases in right posterior cingulate volumes. Decreases that approached significance also were found in volumes of the right caudate, the putamen (bilaterally), and the right superior temporal gyrus. No significant associations were observed among controls.
*Conclusion:* Fetal exposure to elevations in maternal IL-8 led to structural neuroanatomic alterations among cases in regions of the brain consistently implicated in schizophrenia research. In utero exposure to elevations in IL-8 may partially account for brain disturbances commonly found in schizophrenia.



## 1. Introduction

Previous studies have found structural changes throughout the brain in schizophrenia patients compared to non-

* Corresponding author. Temple University, Weiss Hall, 1701 North 13th Street, Philadelphia, PA 19122-6085, United States. Tel.: +1 215 204 1571; fax: +1 215 204 5539.
*E-mail address:* ellman@temple.edu (L.M. Ellman).

0920-9964/$ – see front matter © 2010 Elsevier B.V. All rights reserved.
doi:10.1016/j.schres.2010.05.014

psychiatric controls. Among these studies, increased ventricular size is the most well-replicated structural anomaly found in schizophrenia research (Gur et al., 2007; Wright et al., 2000). Decreases in whole brain volumes and temporolimbic regions also have been repeatedly found among schizophrenia patients (Gur et al., 2007; Wright et al., 2000). Further, studies of individuals who are in the prodrome of schizophrenia also have identified multiple structural brain changes, suggesting that brain disturbances associated with the disorder may have neurodevelopmental origins (Job et al., 2005; Pantelis et al., 2003). Despite these findings, few investigations have sought to determine the contributions of environmental risk factors to neuroanatomical changes found in schizophrenia.

Although genetic factors are believed to substantially contribute to the etiology of schizophrenia, concordance rates approximating 50% between monozygotic twins indicates the presence of substantial environmental influences (Cannon et al., 1998). Among the possible environmental contributors, maternal infections during pregnancy have been repeatedly linked to an increased risk for schizophrenia (Brown and Derkits, 2010). Nevertheless, many infections do not appear to cross the placenta; therefore the damaging influences to the fetal brain seem related to maternal antiviral responses to infection, such as increases in proinflammatory cytokines (Patterson, 2009). In a previous study using the birth cohort of the current investigation, increases in maternal levels of interleukin-8 (IL-8) during the second/third trimesters of pregnancy were associated with increased risk for schizophrenia among offspring (Brown et al., 2004).

Hence, we sought to examine whether fetal exposure to increases in maternal IL-8 during the second/third trimesters results in more pronounced structural brain alterations among individuals diagnosed with schizophrenia and other spectrum disorders (herein referred to as schizophrenia). Our primary hypothesis was that fetal exposure to IL-8 would result in increases in ventricular cerebrospinal fluid (CSF) volume among cases. In addition to the well-replicated association between increases in ventricular CSF and schizophrenia, this hypothesis was derived from animal studies indicating increased ventricular volumes following fetal exposure to immune activation (Patterson, 2009; Wright et al., 2000). Based on previous findings from studies of schizophrenia patients, prodromal research and animal studies, we also predicted that fetal exposure to increased maternal IL-8 would be associated with reduced volumes of temporal lobe regions, particularly in the hippocampus, parahippocampus, and the superior temporal gyrus, and reductions in basal ganglia volumes (Pantelis et al., 2003; Patterson, 2009; Wright et al., 2000). Exploratory analyses were conducted with control participants and on additional regions of interest (ROIs). Analyses of controls were conducted to obtain preliminary findings on whether there are differential vulnerabilities to fetal exposure to IL-8 among cases versus controls, as has been found in other studies (Cannon et al., 2008; Ellman et al., 2009).

## 2. Materials and methods

All subjects provided written informed consent and the study was approved by the Institutional Review Boards of the New York State Psychiatric Institute, the Kaiser Foundation Research Institute, 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 that was based on participants from the Prenatal Determinants of Schizophrenia (PDS) study, which ascertained cases of schizophrenia from a large birth cohort described in detail previously (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 serum samples were collected during the pregnancies and were frozen and stored at $-20\,^{\circ}$ C.

### 2.2. Ascertainment and diagnosis

Case ascertainment and screening were accomplished following computerized record linkage between the CHDS and KPMCP identifiers from inpatient, outpatient, and pharmacy registries of CHDS participants who belonged to KPMCP from 1981 to 1997 (corresponding to the initiation of KPMCP computerized psychiatric registries and to the end of follow-up). Potential cases were diagnosed using 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.

All cases and controls were targeted for neuroimaging assessments in adulthood. DIBS study participants consisted of 23 cases of schizophrenia and 25 controls for MRI acquisition and analysis. Two cases were excluded due to unusable images from movement artifacts. The final sample was comprised of 17 cases and 8 controls with available MRI and available second/third trimester cytokine data. Among the 17 cases, 7 were diagnosed with schizophrenia, 4 with schizoaffective disorder, and 6 with other schizophrenia spectrum disorders. Demographic characteristics of the cases and controls are provided in Table 1. There were no significant differences in any demographic characteristics between cases and controls. There also were no significant differences in any demographic variables between DIBS cases and cases from the PDS study with available cytokine data that were not ascertained as part of the DIBS study (Table 2).

### 2.3. Interleukin-8 assay

Analyses were restricted to second/third trimester IL-8 values, because 1) maternal IL-8 during the second/third trimester was previously associated with schizophrenia in this birth cohort, whereas other proinflammatory cytokines (IL-6, TNF-$\alpha$, IL-1$\beta$) were not associated with schizophrenia (Brown et al., 2004) and 2) we sought to reduce the probability of Type I errors by limiting the number of analyses.

Assays were conducted blind to diagnosis of the offspring and were carried out under Level II biohazard containment conditions. Each serum specimen was thawed and made 2 mM with respect to phenylmethylsulfonyl fluoride, a protease inhibitor, to prevent degradation of cytokines by serum