

# Fetal Hypoxia and Structural Brain Abnormalities in Schizophrenic Patients, Their Siblings, and Controls

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**Background:** Cortical gray matter reductions and cerebrospinal fluid (CSF) increases are robust correlates of schizophrenia, but their relationships to obstetric and other etiologic risk factors remain to be established.

**Methods:** Structured diagnostic interviews, obstetric hospital records, and magnetic resonance imaging scans of the brain were obtained for 64 schizophrenic or schizoaffective patients (representative of all such probands in a Helsinki, Finland, birth cohort), along with 51 of their nonpsychotic full siblings and 54 demographically similar controls without family histories of psychosis.

**Results:** Fetal hypoxia predicted reduced gray matter and increased CSF bilaterally throughout the cortex in patients (gray matter effect sizes,  $-0.31$  to  $-0.56$ ; CSF effect sizes,  $0.25$  to  $0.47$ ) and siblings (gray matter effect sizes,  $0.33$  to  $0.47$ ; CSF effect sizes,  $0.17$  to  $0.33$ ), most strongly in the temporal lobe. Effect sizes were 2 to 3 times greater

among cases born small for their gestational age. Hypoxia also correlated significantly with ventricular enlargement, but only among patients (effect size,  $0.31$ ). In contrast, fetal hypoxia was not related to white matter among patients and siblings, nor to any tissue type in any region among controls. The associations were independent of family membership, overall brain volume, age, sex, substance abuse, and prenatal infection.

**Conclusions:** Fetal hypoxia is associated with greater structural brain abnormalities among schizophrenic patients and their nonschizophrenic siblings than among controls at low genetic risk for schizophrenia. This pattern of results points to a gene-environment interaction account of the disorder's neurodevelopmental pathogenesis.

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**S**TRUCTURAL BRAIN abnormalities are robust correlates of schizophrenia, but their causes have not been conclusively established.<sup>1-3</sup> Neuro-motor and cognitive deficits in preschizophrenic children<sup>4-6</sup> and cortical laminar neuron displacement in schizophrenic patients at autopsy<sup>7-10</sup> suggest that at least some of the anatomical changes associated with schizophrenia are neurodevelopmental in origin.<sup>11</sup> Genetic influences in schizophrenia are substantial,<sup>12</sup> but the mode of inheritance is complex. It involves at least several genes<sup>13</sup> and certain neurally disruptive environmental exposures, such as obstetric complications (OCs).<sup>14-27</sup> Of the many types of OCs found to predict schizophrenia, fetal hypoxia has shown the strongest association, accounting for a greater proportion of liability than exposure to infections during gestation, fetal growth retardation, and other obstetric factors.<sup>27</sup> Because no study using obstetric birth records has found that hypoxic

OCs are more frequent in the first-degree relatives of schizophrenic patients than in the general population,<sup>17-24</sup> these complications do not appear to be consequences of genetic liability to schizophrenia. It is also unlikely that these early influences cause schizophrenia on their own because more than 90% of individuals who experience fetal hypoxia, even in its severe form, do not develop schizophrenia.<sup>17,18,25,26</sup> Hypoxic OCs must thus act additively or interactively with genetic factors in influencing disease liability.<sup>27</sup>

In a prior computed tomography study, we found evidence supporting the gene-environment interaction model with respect to the contribution of fetal hypoxia to subcortical abnormalities in schizophrenic patients.<sup>28</sup> Ventricular-brain ratio increased in association with a history of hypoxia-associated OCs among offspring of schizophrenic parents, but not among offspring of controls, whereas sulcal-brain ratio varied with

## PARTICIPANTS AND METHODS

### SAMPLE

Participants were drawn from the total population of individuals born in Helsinki, Finland, in 1955 and all their full siblings (N = 7840 and N = 12 796, respectively), using methods previously described.<sup>12,32</sup> National computerized databases were used to screen the cohort for a history of psychiatric disorders requiring treatment, and potential probands were randomly selected from this total pool. Eligibility was restricted to probands with a lifetime DSM-III-R<sup>33</sup> diagnosis of schizophrenia or schizoaffective disorder on direct interview. About 75% of those approached gave informed consent and met the inclusion criteria. Studied probands were equivalent to the remainder of the proband population in terms of year of birth, nuclear family size, sex, age at first inpatient admission, history of substance disorder, and work disability, but the studied group had an average of 1.5 more hospital admissions than the nonstudied group.<sup>32</sup> An attempt was made to recruit at least one nonschizophrenic sibling of each studied proband, but this was possible in only 62 of the 80 cases. In addition, 56 nonschizophrenic control subjects (from 28 sibling pairs) were chosen from the same birth cohort, after excluding those with a personal or family history of psychiatric treatment. Control subjects were similar to probands and their siblings on demographic variables. All subjects were interviewed using the Structured Clinical Interview for DSM-III-R disorders<sup>34</sup> administered by psychologists and psychiatric social workers with extensive prior training; siblings and controls were also interviewed on the Cluster A items from the Personality Disorder Examination.<sup>35</sup> Diagnostic reliability was excellent ( $\kappa = 0.94 \pm 0.02$ ),<sup>36</sup> and final diagnoses were made by consensus among 3 independent raters.

Missing obstetric hospital records (n = 21) and/or technical problems with the MRI scans (n = 7) excluded 27 subjects from the analysis. **Table 1** shows that the patient, sibling, and control groups were balanced on substance abuse and major demographic and obstetric variables.

### OBSTETRIC RECORDS

A researcher blind to diagnosis and imaging results used a standard form to code information from the original antenatal clinic and obstetric hospital records on maternal health, fetal monitoring, prenatal and perinatal complications, and neonatal conditions. Obstetric variables used in the analyses were small for gestational age status (ie, birth weight at or below the 10th percentile for a given gestational age), any maternal infection (rubella, influenza, etc) during gestation, and fetal hypoxia. Fetal hypoxia was scored as present if the subject was coded as blue at birth or neonatally or had 2 or more complications that were significantly related to birth or neonatal asphyxia in the overall sample. Complications included umbilical cord knotted or wrapped tightly around the neck, placental infarcts, third-trimester bleeding, preeclampsia, anemia during pregnancy, anorexia during pregnancy, fetal heart rate/rhythm deviations, and breech presentation. Prematurity was removed from the hypoxia definition previously used<sup>18</sup> to permit evaluation of the effects of hypoxia as a function of

developmental status. As nearly all of the subjects born prematurely (ie,  $\geq 2$  weeks) were small for their gestational age, and vice versa, the 2 categories were collapsed together.

### IMAGING PROCEDURES

Images were acquired using a standard dual-echo sequence with 5-mm slice thickness and segmented into gray matter, white matter, and CSF using an adaptive, 3-dimensional, Bayesian algorithm<sup>38</sup> previously validated for this purpose.<sup>39</sup> These volumes were separated by hemisphere and region using operationally defined boundaries for the frontal and temporal lobes.<sup>40</sup> In addition, a "posterior" region was defined as all tissue exclusive of the frontal and temporal lobes. Tracings were performed blindly with respect to diagnosis and birth history, and interrater reliabilities were excellent (intraclass correlations  $> 0.93$ ). Additional details pertaining to MRI acquisition and analysis procedures are provided elsewhere.<sup>32</sup>

### STATISTICAL ANALYSES

The data were analyzed using the general linear-mixed model with repeated measures. We corrected for dependency (ie, correlation) among multiple observations from the same family and the same individual by treating family, and person nested within family, as random variables and adjusting the model error terms accordingly. Measures of gray matter, white matter, sulcal CSF, and ventricular CSF were analyzed separately, with hemisphere and, where appropriate, region (frontal, temporal, posterior) treated as within-subject, repeated-measures variables. We tested the hypothesis that fetal hypoxia is more strongly associated with brain morphology in the presence of genetic susceptibility to schizophrenia by modeling the risk group  $\times$  fetal hypoxia interaction, both overall and in interaction with hemisphere and region, as a fixed-effect predictor. To determine whether these effects vary by prematurity/small for gestational age status, we also modeled the risk group  $\times$  fetal hypoxia  $\times$  small for gestational age status interaction, both overall and in interaction with hemisphere and region. Whenever one of these terms significantly predicted brain volume, contrast analysis was performed to compare subjects with and without a history of hypoxia in each risk group, after collapsing across nonsignificant within-subject dimensions. This approach maintained the hypothesis-wise type I error rate of 0.05 by evaluating a predictor's contribution to a dependent measure only if its effect was significant at the multivariate level. Maternal infection during pregnancy was included as a predictor to control for its possible confounding of the association between hypoxic OCs and brain volumes. There were too few subjects with a history of maternal infection for a meaningful test of its potential interaction with risk group. In addition, the analyses controlled for overall brain volume, age at examination, sex, and history of substance disorder because these individual-difference factors may account for some variability in regional brain volumes. To correct for between-region differences in region of interest size, regional tissue volumes were expressed as percentage ratios of overall regional volumes (eg, frontal gray matter ratio = [frontal gray matter volume / total frontal volume]  $\times 100$ ).

**Table 1. Demographic Characteristics in 3 Comparison Groups\***

Characteristic	Patients (n = 64)	Siblings (n = 51)	Controls (n = 54)	F or $\chi^2$ (P)
Age, y, mean (SD)	40.5 (5.4)	40.3 (5.0)	40.7 (3.1)	0.1 (.87)
Sex				
Male	32 (50)	22 (43)	23 (43)	0.8 (.66)
Female	32 (50)	29 (57)	31 (57)	
Parental social class, mean (SD)	3.1 (1.3)	3.2 (1.4)	3.6 (1.3)	2.0 (.13)
Handedness				
Right	60 (93)	49 (96)	48 (89)	2.2 (.33)
Left/mixed	4 (7)	2 (4)	6 (11)	
Nuclear family size, † mean (SD)	5.3 (1.8)	5.5 (1.8)	5.0 (1.1)	1.5 (.23)
Substance disorder				
Yes	19 (30)	8 (16)	13 (24)	3.1 (.21)
No	45 (70)	43 (84)	41 (76)	
Other Axis I disorder				
Yes	...	11 (22)	12 (22)	0.0 (.94)
No	...	40 (78)	42 (78)	
Cluster A disorder				
Yes	...	5 (10)	0 (0)	5.6 (.02)
No	...	46 (90)	54 (100)	
Total brain volume, mL, mean (SD)	1265 (147)	1271 (146)	1284 (126)	0.3 (.75)
Maternal infection				
Yes	5 (8)	3 (6)	2 (4)	0.9 (.64)
No	59 (92)	48 (94)	52 (96)	
Premature ( $\geq 2$ wk)				
Yes	8 (12)	16 (27)	12 (21)	0.9 (.62)
No	56 (87)	42 (73)	44 (78)	
Small for gestational age				
Yes	6 (9)	6 (12)	5 (9)	0.2 (.89)
No	58 (91)	45 (88)	49 (91)	
Fetal hypoxia				
Yes	15 (23)	13 (25)	12 (22)	0.2 (.92)
No	49 (77)	38 (75)	42 (78)	

\*Data are given as number (percentage) unless otherwise stated. Ellipses indicate not applicable.

†Rahaula scale: range = 1–7.<sup>37</sup>

degree of genetic loading for schizophrenia, but not with the obstetric factors examined. These findings suggest that a genetic factor in schizophrenia may render the fetal brain particularly susceptible to periventricular tissue damage following hypoxia. The interpretability of this evidence is restricted, however, by the limited localizing significance of cerebrospinal fluid (CSF)-based anatomical measures<sup>2</sup> and the questionable generalizability of findings from offspring of mothers with unusually severe forms of schizophrenia.<sup>29</sup> In addition, a magnetic resonance imaging (MRI) study of monozygotic twins discordant for schizophrenia found larger ventricles and smaller temporal lobe volumes in the affected compared with unaffected co-twins, differences that must reflect nongenetic influences<sup>30</sup>; these intrapair differences in ventricular and hippocampal size are related to higher rates of OCs in the affected co-twins.<sup>31</sup>

We have previously reported on differences in regional brain morphology, assessed by MRI, in schizophrenic patients, their nonschizophrenic siblings, and controls at low genetic risk for schizophrenia.<sup>32</sup> Patients and their siblings had reduced gray matter and increased sulcal CSF in the frontal and temporal regions bilaterally, but not in posterior regions. Patients, but not siblings, also showed ventricular enlargement and reduced global white matter compared with controls. As part of this study,

we also collected subjects' original obstetric hospital records. A history of hypoxia-associated OCs, but not prenatal infection or fetal growth retardation, was found to predict an increased risk of early-onset schizophrenia.<sup>18</sup> In this analysis, we used the same samples to determine whether fetal hypoxia was differentially related to ventricular enlargement and temporal-lobe volume reduction among patients and siblings at elevated risk for schizophrenia, compared with controls at low genetic risk.

## RESULTS

### FETAL HYPOXIA

Mixed-model, repeated-measures analyses of regional and hemispheric gray matter, white matter, and CSF brain ratios showed that fetal hypoxia is a significant predictor of gray matter ( $F_{1,111} = 14.6, P < .001$ ) and total sulcal CSF ( $F_{1,144} = 8.3, P = .005$ ). Analyses also showed that fetal hypoxia interacted significantly with risk group in the prediction of overall gray matter ( $F_{2,95} = 6, P = .003$ ), with nonsignificant trends in this direction for overall sulcal CSF ( $F_{2,125} = 2.7, P = .07$ ) and overall ventricular CSF ( $F_{2,135} = 2.7, P = .07$ ). For both gray matter ( $F_{10,785} = 6.8, P < .001$ ) and sulcal CSF ( $F_{10,785} = 7.0, P < .001$ ), the risk group  $\times$  fetal hypoxia interaction term varied signifi-

**Table 2. Regional Gray (GM) and White Matter (WM), Sulcal (SCSF), and Ventricular Cerebrospinal Fluid (VCSF) Brain Ratios by Risk Group and Fetal Hypoxia\***

Tissue	Patients			Siblings			Controls		
	No Hypoxia (n = 49)	Hypoxia (n = 15)	Effect Size†	No Hypoxia (n = 38)	Hypoxia (n = 13)	Effect Size†	No Hypoxia (n = 42)	Hypoxia (n = 12)	Effect Size†
GM									
Frontal	52.8 ± 0.5	49.9 ± 0.8	-.384‡	53.8 ± 0.6	51.7 ± 0.8	-.332§	53.8 ± 0.7	54.3 ± 0.9	.071
Temporal	62.1 ± 0.5	58 ± 0.8	-.555‡	62.5 ± 0.6	59.4 ± 0.8	-.472‡	63.2 ± 0.7	63.5 ± 0.9	.052
Posterior	53.2 ± 0.5	50.9 ± 0.8	-.308§	52.2 ± 0.6	49.8 ± 0.8	-.372§	52.1 ± 0.7	52.5 ± 0.9	.064
WM	35 ± 0.4	34.5 ± 0.6	-.109	35.1 ± 0.4	35.7 ± 0.5	.151	35.8 ± 0.4	35.7 ± 0.6	-.025
SCSF									
Frontal	12.1 ± 0.7	16.1 ± 1.0	.451‡	11.3 ± 0.8	12.7 ± 1.0	.171	10.1 ± 0.8	10.3 ± 1.1	.026
Temporal	7.1 ± 0.7	11.3 ± 1.0	.471‡	6.4 ± 0.8	8.9 ± 1.0	.331§	5.3 ± 0.8	5.2 ± 1.1	-.006
Posterior	7.6 ± 0.7	9.8 ± 1.0	.245	7.8 ± 0.8	9.7 ± 1.0	.245	7.4 ± 0.8	7.3 ± 1.1	-.015
VCSF	1.7 ± 0.2	2.5 ± 0.3	.314§	1.5 ± 0.2	1.8 ± 0.3	.114	1.6 ± 0.2	1.3 ± 0.3	-.109

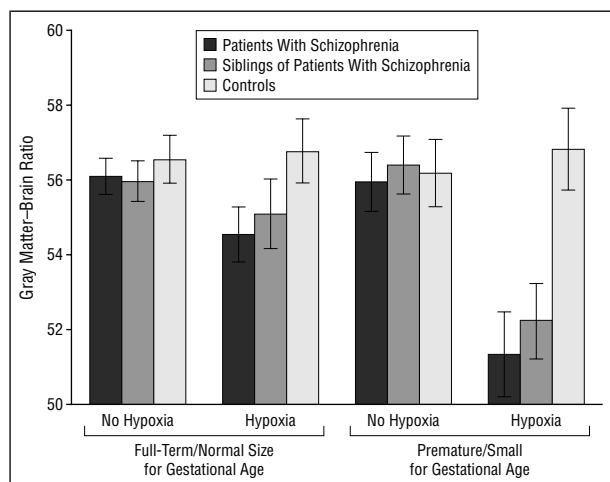
\*Values are least square mean ± SEM adjusted for total brain volume, age, sex, substance abuse, maternal infection during pregnancy, prematurity/small for gestational age status, and family membership.

†Effect size is defined as the difference in the means of the group with hypoxia compared with the group without, divided by their pooled SD.

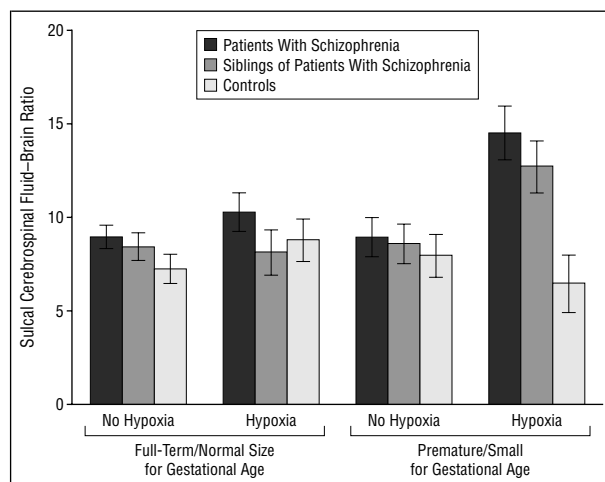
‡P < .001.

§P < .01.

||P < .05.



**Figure 1.** Least square mean ± SEM overall gray matter–brain ratios of schizophrenic patients, siblings, and controls, as a function of fetal hypoxia and small for gestational age status. Of the 64 probands, 51 were normal size at birth (10 with and 41 without a history of fetal hypoxia), and 13 were small for their gestational age (5 with and 8 without a history of fetal hypoxia). Of the 51 siblings, 37 were normal size at birth (8 with and 29 without a history of fetal hypoxia), and 14 were small for gestational age (5 with and 9 without a history of fetal hypoxia). Of the 54 controls, 42 were normal size at birth (8 with and 34 without a history of fetal hypoxia), and 12 were small for gestational age (4 with and 8 without a history of fetal hypoxia).



**Figure 2.** Least square mean ± SEM overall sulcal cerebrospinal fluid–brain ratios of schizophrenic patients, siblings, and controls as a function of fetal hypoxia and small for gestational age status. Group sample sizes were as given in the legend to Figure 1.

cantly as a function of region, but not as a function of hemisphere or region within hemisphere. As shown in **Table 2**, while there were significant reductions in gray matter associated with fetal hypoxia in all regions among patients and siblings, the magnitude of this association was greatest in the temporal lobe for both groups. The same pattern was present with regard to regional sulcal enlargement among patients, while among siblings, hypoxia was significantly associated with sulcal enlargement only in the temporal lobe. Fetal hypoxia was also associated with a significant increase in ventricular CSF,

but only among patients. In contrast, fetal hypoxia was not significantly related to white matter in any group and was not significantly related to any tissue type in any region for controls.

#### PREMATURITY/SMALL FOR GESTATIONAL AGE STATUS

There was a main effect of small for gestational age status on gray matter ( $F_{1,125}=4.8, P=.03$ ) and sulcal CSF ( $F_{1,152}=3.8, P=.05$ ). The risk group × fetal hypoxia interaction term varied nonsignificantly as a function of small for gestational age status for gray matter ( $F_{5,98}=1.9, P=.10$ ), with a significant trend in this direction for sulcal CFS ( $F_{5,128}=2.5, P=.04$ ), depicted in **Figure 1** and **Figure 2**, respectively. The associations of fetal hypoxia with gray matter reduction and sulcal

enlargement in the patients and their siblings were substantially greater (ie, the effect sizes were 2-3 times larger) among those born prematurely and/or small for their gestational age. Among subjects born at full term and/or at normal size for their gestational age, fetal hypoxia was associated with a significant reduction in gray matter only in the patients. In contrast, small for gestational age status was unrelated to gray matter or sulcal CSF in the absence of hypoxia, and there were no significant relationships between fetal hypoxia and gray matter or sulcal CSF in the controls, regardless of developmental status at birth.

### PRENATAL INFECTION

Infection had a significant overall main effect on gray matter ( $F_{1,108}=7.8$ ,  $P=.006$ ) and sulcal CSF ( $F_{1,137}=6.2$ ,  $P=.014$ ), but not on white matter or ventricular CSF. Subjects with a history of maternal infection during gestation had lower gray matter- and higher sulcal CSF-brain ratios than those who did not (mean  $\pm$  SEM,  $54.3 \pm 0.7$  vs  $56.3 \pm 0.3$  for gray matter;  $10.5 \pm 1.0$  vs  $8.0 \pm 0.4$  for sulcal CSF).

### COVARIATES

Total brain volume significantly predicted gray matter ( $F_{1,149}=19.1$ ,  $P<.001$ ), white matter ( $F_{1,132}=29.1$ ,  $P<.001$ ), and ventricular CSF ( $F_{1,128}=4.8$ ,  $P=.03$ ) volumes. Age at scanning and substance abuse significantly predicted gray matter volume ( $F_{1,138}=6.7$ ,  $P=.01$ ;  $F_{1,100}=3.6$ ,  $P=.04$ , respectively). Sex did not significantly predict any volumes after controlling for total brain volume.

### COMMENT

The principal finding of this study is that a history of fetal hypoxia is associated with increased structural brain abnormalities among schizophrenia patients and their nonschizophrenic siblings, but not among controls at low genetic risk for the disorder. In the following paragraphs, we consider the major competing explanations of our findings followed by their potential implications.

First, the association between fetal hypoxia and altered neuroanatomy could be accounted for by other OCs that both increase risk for schizophrenia and disrupt the brain via mechanisms other than, or in addition to, oxygen insufficiency. However, we considered the 2 most prominent such candidates, prenatal infection and fetal growth retardation, and found that neither was significantly correlated with either fetal hypoxia or adult schizophrenia. Furthermore, controlling for these 2 factors statistically did not modify the significance or magnitude of the associations between fetal hypoxia and brain morphology in patients or siblings. Still, some cases of fetal growth retardation may be expected to stem from conditions, such as placental insufficiency, that cause mild but chronic fetal hypoxia.<sup>41</sup> In keeping with this view, the associations of fetal hypoxia with brain morphology were greatly magnified among the patients and siblings born small for their gestational age. However, because fetal growth retardation did not predict significant alter-

ations in brain morphology in the absence of hypoxia, growth retardation per se does not compete with hypoxia as the mechanism underlying these associations.

One could also argue that our findings suggest an influence other than hypoxia because some of its well-characterized macroscopic brain sequelae, such as periventricular white matter damage, were not observed. However, the neural sequelae of hypoxia are numerous and dependent on the severity and timing of the insult. At the cellular level, they vary in severity from alterations in neurite outgrowth to neuronal cell death.<sup>42</sup> Only in the latter case would a loss of both gray and white matter be expected. In the former case, immature neurons may survive the hypoxic insult but still have a compromised elaboration of synaptic interconnections.<sup>42</sup> Studies in fetal sheep have shown that hypoxia secondary to chronic placental insufficiency is associated with reduced cortical thickness and increased cortical neuronal density, without any observable neuronal loss or white matter damage.<sup>43</sup> These reductions in neuropil volume should manifest as reductions in gray but not white matter volume at the macroscopic level. The pattern of morphologic changes associated with hypoxia in this study is thus compatible with an animal model of chronic fetal hypoxia. Also supporting this interpretation is the fact that more than 80% of subjects in the fetal hypoxia group were positive for markers of both prenatal and birth asphyxia.

Another possibility is that the effects of hypoxia would be confounded with shared genetic or environmental influences that increase the likelihood of hypoxic complications among patients and their unaffected siblings. However, the siblings did not have higher rates of hypoxia-associated OCs than the controls,<sup>18</sup> indicating an absence of covariation between these OCs and genetic risk status. Although covariation between hypoxia and a shared environmental influence cannot be excluded entirely, twin and adoption studies have shown that shared environment plays a negligible role in the overall etiology of schizophrenia.<sup>12,44</sup> Moreover, it is difficult to imagine a systematic environmental influence that would manifest as greater susceptibility to hypoxic-ischemic brain injury and that would be shared by siblings discordant for schizophrenia but not by demographically matched controls. The most plausible of such candidates are prenatal viral infection and fetal growth retardation, which were neither more common in patients and siblings nor responsible for the significant hypoxia effects.

We can also exclude the possibility that our findings are a consequence of selecting a nonrepresentative sample of probands. This study used a random, population-based sampling method that resulted in excellent correspondence between studied and nonstudied probands on major demographic and clinical variables. Furthermore, because the sibling and control groups were well matched on the presence of major psychiatric disorders, our findings are not due to an excess of nonschizophrenia-related mental illness among siblings.

It would thus appear that hypoxia-associated OCs are related in some manner to the neurodevelopmental pathogenesis of schizophrenia. In the context of a dis-



order with polygenic inheritance,<sup>45</sup> OCs may act either additively or interactively with genetic factors in increasing risk for schizophrenia on a continuum of liability.<sup>27</sup> The additive model predicts that hypoxia should have an equivalent degree of influence on continuous markers of disease liability, regardless of the degree of genetic background for the disorder. The interaction model predicts that fetal hypoxia should have a differential relationship with continuous markers of disease liability in those at elevated genetic risk for schizophrenia compared with those at low genetic risk. Our finding that fetal hypoxia is associated with increased signs of brain abnormalities in both patients and their siblings, but not among low-risk controls, is thus consistent with the gene-environment interaction model. Also supporting this model is our earlier study, which found that hypoxic complications predict increased risk for schizophrenia and greater ventricular enlargement among offspring of schizophrenic parents, but not among offspring of nonschizophrenic parents.<sup>20,28</sup> Cortical sulcal enlargement did not vary by obstetric history among those at genetic risk for schizophrenia in the Danish study,<sup>28</sup> as it did in the present study, which most likely reflects the greater reduction in signal at the cortical surface (due to partial volume artifacts) associated with computed tomography compared with MRI.

The gene-environment interaction model makes 2 additional predictions that can be tested with this sample: (1) fetal hypoxia should occur more frequently among schizophrenic patients than among their siblings, and (2) the association between fetal hypoxia and continuous liability indicators should be differential in the patients compared with their siblings. While rates of fetal hypoxia did not differ by risk group in this study, a prior report on this sample found that hypoxia-associated OCs were elevated among cases with an early age at onset, but not among later-onset cases or among siblings of either group.<sup>18</sup> Moreover, the odds of early-onset schizophrenia increased 2.9 times per hypoxic OC within families.<sup>18</sup> Because this report examined the relationship of OCs and brain morphology rather than diagnosis, and because of the limited sample sizes available, early-onset and later-onset cases were collapsed together in the analyses. The fact that most patients with a history of fetal hypoxia were early-onset cases raises the possibility that hypoxia exposure is confounded with other factors that determine age at onset. However, the associations between fetal hypoxia and brain morphology remained significant after the patients' data were reanalyzed with age at onset as an additional covariate ( $F_{1,54}=7.8$ ,  $P=.007$  for gray matter;  $F_{1,54}=4.8$ ,  $P=.03$  for sulcal CSF; and  $F_{1,54}=7.9$ ,  $P=.007$  for ventricular CSF).

Consistent with the second prediction, the effect of hypoxia was significantly greater among patients than siblings for both gray matter ( $F_{6,535}=6.53$ ,  $P<.001$ ) and sulcal CSF ( $F_{6,535}=6.20$ ,  $P<.001$ ) and was present only among patients for ventricular CSF (Table 2). Thus, while unaffected siblings show some sensitivity to the schizophrenia-promoting effects of fetal hypoxia, this sensitivity differs from that observed in patients both quantitatively (for cortical measures) and qualitatively (for ventricular enlargement).

These findings add to the growing evidence that at least some of the brain abnormalities in schizophrenic patients are neurodevelopmental in origin.<sup>11</sup> That ventricular enlargement and reduced cortical gray matter volume were correlated with an adverse condition at birth clearly suggests an early origin for these abnormalities, although it in no way excludes participation of later neurodevelopmental<sup>46</sup> or neurodegenerative<sup>47</sup> processes. It also appears likely that genes predisposing to schizophrenia may render the fetal brain especially vulnerable to hypoxic OCs. This finding encourages the search for genes that heighten the brain's vulnerability to hypoxic/ischemic neuronal injury.

This study has several limitations. We used T2-weighted images with a large slice thickness (5 mm), which are more prone to partial volume artifact than higher-resolution, T1-weighted images. Such effects are magnified in the presence of sulcal enlargement and may therefore interact with diagnostic status. However, because the primary impact of a partial volume artifact is to lower the signal-to-noise ratio, thereby reducing the power to detect true associations, the presence of such an interaction in these data would most likely have led to an underestimation of effect sizes in the patient and sibling groups. This study also employed relatively gross anatomical divisions, making it unclear whether the associations between hypoxia and gray matter loss in the posterior region reflect volume reductions in subcortical structures, occipital-parietal cortices, or both. An effect on posterior gray matter appears likely because approximately 80% of the volume of the posterior region refers to the occipital-parietal cortex. An association of hypoxia with subcortical abnormalities also seems probable given its correlation with ventricular enlargement, which in schizophrenia is associated with periventricular gray matter reduction.<sup>48,49</sup>

Because most subjects with a history of fetal hypoxia were positive for markers of both prenatal and perinatal hypoxia, we were unable to examine whether hypoxia occurring at different times in development (expected to result in differential patterns of regional brain injury<sup>50,51</sup>) is differentially relevant to structural brain abnormalities in schizophrenia. In addition, our definition of hypoxia exposure was limited to complications that were recorded in the birth records of the Finnish health system during the 1950s. While these records are of high quality and yield obstetric measures that are clearly superior to those obtained via retrospective maternal interview, more direct, quantitative methods for assaying fetal blood oxygenation<sup>52,53</sup> would permit a more sensitive test of our hypotheses.

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