Diminished Cerebral Inhibition in Neonates Associated With Risk Factors for Schizophrenia: Parental Psychosis, Maternal Depression, and Nicotine Use

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Diminished inhibitory gating of cerebral auditory evoked responses is transmitted in families with psychoses as an endophenotype related to the genetic risk for these illnesses. To assess whether the endophenotype is already expressed in infants of parents with psychotic illness and to assess effects of other known risk factors for schizophrenia, ie, maternal cigarette smoking and depression, inhibitory gating of cerebral auditory evoked responses was evaluated by comparing the P1 evoked responses to the first and second of paired auditory stimuli. Cerebral evoked responses were recorded during active sleep from 22 infants with a parent diagnosed with a psychotic illness and 129 infants with parents with no such history. Of these infants, 25 were prenatally exposed to nicotine (16 from the comparison group and 9 from the group with parental psychosis). Mothers of 35 infants had diagnoses of major depressive disorder. Parental psychosis (P = .032) and exposure to maternal smoking (P = .012) both resulted in diminished inhibitory gating in infant offspring. Compared to infants of mothers who did not smoke and who had neither parental psychosis nor maternal depression, diminished inhibitory gating was observed in infants with parental psychosis (P = .027) and in infants with maternal depression (P = .049). Diminished inhibitory gating of auditory evoked response in infants who have risk factors for schizophrenia mirrors reports of its familial transmission in adults. The results further indicate that the phenotypic expression of familial genetic and environmental risks for psychosis is already manifest very early in development.

Key words: child development/evoked potentials/auditory/sleep/REM

Introduction

Schizophrenia has been postulated to be a neurodevelopmental brain illness resulting from early genetic and environmental insults.1–4 However, the early phenotypic expression of risk has been obscure because schizophrenia is generally not fully expressed until early adulthood. Primary prevention strategies for neurodevelopmental brain illnesses require identification of the developmental windows in which the pathology occurs and the neuronal mechanisms that are affected in any particular window. For an illness whose full clinical manifestation is not until early adulthood, there are likely a number of such windows including developmental changes in gene expression as the psychosis emerges, but many of the genes associated with schizophrenia appear to be functioning maximally during fetal brain development, and environmental insults during this period also appear to be critical.5 If initial brain development during fetal life is indeed a critical period, then neonatal brain studies are needed to confirm which aspects of the pathology have already occurred by birth.

Epidemiological studies have identified at least 4 parental risk factors for the later development of schizophrenia in their offspring: parental genetic risk and in utero exposure to maternal smoking, depression, and infection.6–9 Genetic risk is estimated to account for much of the familial transmission of schizophrenia, although no single gene has been isolated.6 The OR of schizophrenia occurring in the offspring of a psychotic parent is 2.6 in a recent Finnish study.7 Although maternal depression itself did not increase the risk for schizophrenia, offspring with parental risk for schizophrenia whose mother had depressed mood during pregnancy have an OR of schizophrenia of 9.4, indicative of an additive effect of the 2 risk factors. A similar additive effect was noted in another epidemiological study for a maternal infection, pyelonephritis, and parental history of schizophrenia.8 Nicotine use during pregnancy was associated with increased risk for the development of psychotic symptoms in the offspring in yet another epidemiological study.9

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Because schizophrenia generally does not occur until adolescence or early adulthood, the possible effects of these risk factors must be observed on other brain functions during development. It has been proposed that much of the genetic risk for schizophrenia is first manifest as endophenotypes, deficits in specific brain functions that predispose individuals for the later expression of the illness. One endophenotypic expression of the genetic risk for schizophrenia is diminished inhibitory gating of the cerebral auditory evoked response to repeated auditory stimuli. The responses to paired stimuli are often used to demonstrate inhibition: A diminished response to the second stimulus suggests the effects of inhibitory mechanisms that have been activated during the response to the first stimulus. The amount of decrement of response to the second stimulus is a measure of the strength of the inhibition.

Although psychosis is expected to occur in only about 10% of the offspring of a parent with schizophrenia, abnormalities in inhibitory gating of auditory response occur in about half their offspring, consistent with more penetrant genetic transmission. The endophenotype is also transmitted in families with bipolar disorder, where it is related to the risk for psychotic symptoms. Diminished inhibitory gating has been related to variants in several genes associated with the risk for schizophrenia, including CHRNA7, the gene for the α7-nicotinic cholinergic receptor subunit, and COMT, the gene for catechol-O-methyltransferase.

Inhibitory gating of the cerebral response to a repeated auditory stimulus is a passive automatic response, which is associated with the brain’s ability to pay attention to targeted stimuli and to ignore less important repeated stimuli. The first prominent wave in the auditory evoked response, termed P1 or P50 because it is positive and has a nominal latency of 50 ms after the stimulus in adults, is often used for analysis. Stimuli are presented in pairs. Rodent models of the responses to paired stimuli have shown that inhibitory gamma-aminobutyric acid (GABA) neuronal mechanisms, both GABA_A receptor–mediated postsynaptic inhibition of cell discharge and GABA_B receptor–mediated presynaptic inhibition of glutamate release, are activated during the response to the first stimulus of the pair (S1). Underlying abnormalities in neural oscillatory patterns are critically involved. At the 500 ms interval between stimuli used in this study, prolonged activation of cerebral inhibitory neurons by cholinergic stimulation from the midbrain is required for inhibition of the response to the second stimulus. The α7-nicotinic receptor is the principal cholinergic receptor involved. The second stimulus of the pair (S2) elicits a diminished response because of the activity of these inhibitory mechanisms. The ratio of P1 amplitudes (S2:S1) assesses the strength of the inhibition, with lower values indicating increased inhibition. In a multisite study of normal adults, the ratio for patients with schizophrenia (mean [SD] 0.61 [0.48], n = 181) was significantly elevated over the value found in normals (mean [SD] 0.38 [0.32], n = 333; d' = 0.6). The loss of inhibition in schizophrenia is consistent with evidence in postmortem brain for the loss of expression of receptors, peptides, and synthetic enzymes associated with the function of hippocampal and neocortical inhibitory neurons.

Because newborn infants spend most of their time in active sleep, the analog to the rapid eye movement (REM) sleep of adults, we first showed that inhibitory gating occurs during REM sleep in adults and that persons with schizophrenia show deficits that are identical to those previously characterized in waking, in order to validate that the phenotype associated with risk for schizophrenia is manifest in this behavioral state as well as in waking. Active sleep has the benefit of its associated atonia, which prevents the infants from pulling the electrodes away from their head, decreased adrenergic tone, which reduces anxiety- and stress-associated interference with sensory gating, and unconsciousness, which permits presentation of many more pairs of stimuli, a minimum of 90 in this study, than are tolerable during waking. This inhibitory brain function is already present to a substantial degree in normally developing newborn infants, although the P1 of infants has a larger amplitude and longer latency than the corresponding P1 or P50 recorded from adults. Test-retest reliability of recordings from neonatal infants across different days has been demonstrated, with intraclass correlation for the S2:S1 P1 ratio of 0.84.

The primary purpose of this study was to determine if infants of psychotic parents, who have presumed increased genetic risk for psychosis, already show the cerebral inhibitory deficit associated with this risk in studies of adults. None of the mothers in this study had infectious illnesses that were detected clinically, but maternal depression and nicotine use were frequently present. The high comorbidity of nicotine abuse in schizophrenia and the high prevalence of depression in pregnancy mean that these factors co-occur commonly in any sample of mothers drawn from the community. Therefore, the effects of these factors on the infants’ brain physiology were also assessed.

Methods

Subjects

Psychotic parents were identified through the Obstetrical Service of Denver Health Medical Center, a large urban public hospital, as part of an ongoing longitudinal study. Thirty infants were identified. Eight infants were excluded because they did not remain in active sleep long enough for electrophysiological recording. The 22 infants with usable data came from 10 parents with schizophrenia (Diagnostic and Statistical Manual of Mental Disorders [Fourth Edition] [DSM-IV] 295; 6 mothers and
4 fathers), 13 mothers with bipolar disorder with psychotic features (DSM-IV 296.44, 296.54), and 2 mothers with major depressive disorder with psychotic features (DSM IV 295.34). All lifetime diagnoses were made from a Structured Clinical Interview for DSM-IV (SCID-I) diagnostic interview. All mothers and 12 fathers were interviewed. Conception was estimated from the last menstrual period. Postconceptual age at birth ranged from 33 to 38 weeks. Infants were recorded within 6 months of birth.

A state birth registry was used to contact women who had recently delivered infants and who resided in the same zip codes as the psychotic women. These women were also interviewed using the SCID-I diagnostic interview. Infants of 169 women were recorded. Sixteen infants were excluded because they did not stay in active sleep long enough for electrophysiological recording. For comparison with the psychotic women, infants from 94 women who did not have mental illness and infants from 35 women who had major depressive disorder were selected. Infants from 24 women with substance abuse other than nicotine or other psychiatric disorders were excluded. Eighty-one fathers were interviewed; 4 had major depressive disorder. No parent in this group had a psychotic disorder or a known family history of psychosis. As with the infants of psychotic mothers, these infants were developmentally normal at birth, postconceptual age at birth ranged from 33 to 38 weeks, and infants were recorded within 6 months of birth. Table 1 presents demographic and other descriptive information regarding parents and infants.

Based upon maternal report, all infants were developmentally normal and had no diagnosed illnesses. Infants of parents with a psychotic disorder did not differ from the others on postconceptual age, $t_{149} = -0.10, P = .91$, or gender distribution $\chi^2_{1} = 0.17, P = .68$. The postconceptual age of the male infants was 52.8 (5.3) weeks and of the female infants was 51.8 (4.2) weeks (mean [SD]). Mothers were asked about smoking during pregnancy. Those who smoked reported an average of 6 (3) cigarettes per day, with no difference in intensity between mothers from different diagnostic groups.

The study was approved by the Colorado Multiple Institutional Review Board. The parents gave their informed consent to be interviewed, and the mothers consented for their children to be recorded.

Electrophysiological Recording

Gold-plated electrodes (Grass Instruments; West Warwick, Rhode Island), attached with Ten20 conductive paste (DO Weaver; Aurora, Colorado) and adhesive medical tape, were used to record a continuous electroencephalogram (EEG) from the vertex (Cz) referenced to the forehead, a bipolar electrooculogram, and a submental electromyogram. A Grass breathing-effort strap was used to record respiration. Signals were recorded using NuAmps (Neuroscan Labs, Sterling, Virginia). EEG signals were amplified 5000 times and filtered between 0.05 and 100 HZ; electrooculogram signals were amplified 1000 times and filtered between 1 and

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<thead>
<tr>
<th>Parents</th>
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<th>No History</th>
<th>Maternal Depression</th>
<th>Parental Psychosis</th>
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<td></td>
</tr>
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<td>15 (5)</td>
<td>12 (6)</td>
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<td>$N = 22$</td>
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<td>Fathers</td>
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<td></td>
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<tr>
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<td>31 (6)</td>
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<td>8</td>
<td>9</td>
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<tr>
<td>Both</td>
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<td>26</td>
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<td>6</td>
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<td>Weight at birth (g)</td>
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<td>3326 (694)</td>
<td>3129 (609)</td>
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<tr>
<td>Postconceptual age at birth (wk)</td>
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<td>37 (2)</td>
<td>38 (1)</td>
<td>38 (2)</td>
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<tr>
<td>Age at testing (wk)</td>
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<td>12 (5)</td>
<td>13 (5)</td>
<td>12 (6)</td>
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<td>Race/ethnicity</td>
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<td></td>
<td></td>
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<td>African American</td>
<td>6</td>
<td>3</td>
<td>1</td>
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<td>Asian</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
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<td>113</td>
<td>68</td>
<td>31</td>
<td>14</td>
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<tr>
<td>Mixed</td>
<td>11</td>
<td>5</td>
<td>3</td>
<td>3</td>
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</tbody>
</table>

Note: Means (SD) are shown; there were no significant differences between groups.
200 Hz; and electromyogram signals were amplified 10,000 times and filtered between 1 and 200 Hz. Breathing strap output was amplified 100 times and filtered between 0.05 and 30 Hz. Sampling rate was 1000 Hz. The continuously recorded data were converted from the Scan 4.1 software (Neuroscan Labs) format to the ASCII format. MatLab (Mathworks, Natick, Massachusetts) software was used for further analysis.

While infants were asleep, auditory stimuli (0.04 ms clicks) were presented through 2 speakers positioned at either side of the infants’ head, 0.5 m from the ears. The peak loudness of the clicks was 85 dB sound pressure level, measured by the output of a sound meter (Radio Shack 39-2055) monitored on an oscilloscope. Infants are generally resistant to awakening by sounds with this intensity. Clicks were presented in pairs, with intrapair interval of 0.5 s and interpair interval of 10 s. Recording continued for as long as the infant remained asleep. The continuous recording was visually inspected offline in 20-s epochs in order to determine sleep state. Active sleep was identified by the presence of REMs, low amplitude, high-frequency activity in the EEG record, and irregular breathing as recorded by the breathing strap. Infants must have had at least 15 min of continuous active sleep to be included in the study; the first 15 min of the identified active sleep period was used for data analysis. Single-trial evoked potentials were extracted from 100 ms before each click to 200 ms following each click. Trials in which the voltage exceeded ±75 μV were excluded from further analysis. Fewer than 25% of trials were excluded for any infant. REMs, which cause EEG artifacts during active sleep greater than 75 μV in adults, do not fully develop until after 6 months of age. The averaged waveforms computed from these single trials were band-pass filtered between 10 and 50 Hz in order to accentuate middle latency components. Separate averages were calculated for the response to the first (S1) and to the second click (S2) in the pairs. The amplitude and latency of the largest positive peak (P1) between 50 and 100 ms following either stimulus that was preceded by a negative trough were identified and measured by a computer algorithm. These latency windows are longer than that used for adults because the P1 response is larger and has a longer latency in infants.

From the amplitudes of the S1 and S2 evoked responses, the amplitude of P1 evoked by the second click of each pair divided by the average amplitude of P1 evoked by the first click was then calculated (S2/S1). Lower ratios are indicative of greater inhibition of the P1 auditory evoked response to the second stimulus in the paradigm.

**Data Analysis**

Two-way ANOVAs with parental mental illness and maternal smoking as independent factors and the infant postconceptual age as a covariate were used to assess associations of these factors with the P1 amplitude and latency in response to the first and second stimulus and their ratio. SDs are shown for all mean values. All significance levels are 2 tailed.

**Results**

**Association Between Infants’ Auditory Evoked Responses and Parental History of Psychosis**

The averaged evoked response to repeated auditory stimuli was recorded from 151 infants within 6 months of their birth (figure 1). Neither the infants’ age since birth (mean [SD] 13.3 [4.8]; range = 3–28 wk) nor their age since conception (mean 52.3 [4.8]; range = 41–64 wk) significantly affected the amplitude of either of the P1 responses or the ratio of the second to the first response. Postconceptual age was used as a covariate in subsequent analyses; the development of sleep physiology in neonates is related to postconceptual age, rather than to age since birth because of different levels of gestational maturity at delivery.

For the primary intended comparison between infants with psychotic parents and infants with nonpsychotic postconceptual age as a covariate were used to assess associations of these factors with the P1 amplitude and latency in response to the first and second stimulus and their ratio. SDs are shown for all mean values. All significance levels are 2 tailed.
parents, excluding infants whose mothers were depressed or cigarette smokers, we achieved a sample of 13 infants with psychotic parents and 83 infants with nonpsychotic parents. Based on $d' = 0.6$ for the effect of schizophrenia on P50 S2:S1 ratio in adults, the sample provided 0.72 power for the comparison of P1 S2:S1 ratio between the 2 groups of infants, $\alpha = .05$, 2 tailed. We found a significantly increased P1 S2:S1 ratio in the infants with psychotic parents (mean 0.66 [0.31 SD]) compared with the infants with nonpsychotic parents (mean 0.44 [0.33 SD], $t_{94} = 2.25, P = .027$). Neither S1 nor S2 P1 amplitudes alone were significantly different between these 2 groups.

**Effects of Maternal Nicotine Use on Infants’ Inhibition of Auditory Evoked Response**

Further analyses were performed to include all infants who were studied. A 2-way ANCOVA of P1 S2:S1 ratio that considered both parental psychosis and maternal smoking as risk factors was significant ($F_{4,146} = 4.54, P = .0018$). In the sample of the 22 parents with psychotic illnesses, 9 of the mothers smoked during the pregnancy compared with 16 of 129 nonpsychotic women (41% vs 12%). Associations with P1 S2:S1 ratio were significant for both parental psychosis ($F_{1,146} = 4.69, P = .032$) and maternal smoking ($F_{1,146} = 6.42, P = .012$; figure 2). There was no significant interaction.

**Association Between Infants’ Auditory Evoked Responses and Maternal Depression**

In the nonsmoking comparison group, 35 mothers had a maternal diagnosis of major depressive disorder. Infants of mothers who did not smoke and who had neither parental psychosis nor maternal depression had a mean (SD) P1 S2:S1 ratio of 0.44 (0.33) not significantly different from normal adults. Compared with these infants, elevated P1 S2:S1 ratios were observed in infants with maternal depression, mean 0.58 (0.33); $t_{111} = 1.99, P = .049$). The P1 S2:S1 ratios of the infants of depressed mothers were not significantly different from the ratios of the infants with parental psychosis or maternal nicotine use (figure 2; table 2).

**Table 2. P1 Auditory Evoked Potential Responses to Paired Stimuli in Infants**

<table>
<thead>
<tr>
<th>Parental Mental Disorders and Smoking Status</th>
<th>P1 Response to First Stimulus (S1) (µV)</th>
<th>P1 Response to Second Stimulus (S2) (µV)</th>
<th>P1 Latency After S1 (ms)</th>
<th>P1 Latency After S2 (ms)</th>
<th>P1 Ratio (S2:S1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No maternal smoking</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No parental mental health diagnosis (N = 83)</td>
<td>2.21 (1.39)</td>
<td>1.03 (0.95)</td>
<td>77.66 (18.77)</td>
<td>77.37 (19.32)</td>
<td>0.44 (0.33)</td>
</tr>
<tr>
<td>Maternal or paternal psychosis (N = 13)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2.21 (1.19)</td>
<td>1.25 (1.12)</td>
<td>81.00 (17.90)</td>
<td>78.31 (17.66)</td>
<td>0.66 (0.31)</td>
</tr>
<tr>
<td>Maternal major depression (N = 30)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2.21 (1.16)</td>
<td>1.42 (1.33)</td>
<td>75.13 (18.43)</td>
<td>73.87 (20.69)</td>
<td>0.58 (0.33)</td>
</tr>
<tr>
<td>Maternal smoking</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No parental mental health diagnosis (N = 11)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1.97 (1.28)</td>
<td>1.15 (0.87)</td>
<td>79.06 (15.22)</td>
<td>80.06 (15.04)</td>
<td>0.66 (0.39)</td>
</tr>
<tr>
<td>Parental psychosis or maternal depression (N = 14)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>1.98 (1.47)</td>
<td>1.50 (0.93)</td>
<td>81.22 (17.01)</td>
<td>83.22 (16.87)</td>
<td>0.88 (0.31)</td>
</tr>
</tbody>
</table>

*Note: Means (SD) are shown. For the P1 S2:S1 ratio significant differences were found for all groups compared with mothers with no mental health diagnosis who did not smoke: <sup>a</sup>$t_{94} = 2.25, P = .027$; <sup>b</sup>$t_{111} = 1.99, P = .049$; <sup>c</sup>$t_{92} = 2.03, P = .045$; <sup>d</sup>$t_{95} = 4.65, P = .00011$. None of the other groups differed significantly from each other. There were no significant associations of risk factors with S1 or S2 amplitude or latency.*
Of the 30 depressed women who did not smoke, 24 were currently depressed and 6 had only previous histories of depression. There was no significant association of this classification with their infants’ P1 S2:S1 ratios, (current depression mean [SD] 0.60 [0.32]; previous depression only 0.50 [0.38]).

Because of nonrandom mating between human beings, the risk factors were not uniformly distributed between parents. There were 21 mothers with a psychotic illness and 4 such fathers, but only 1 parental pair with a psychotic father and a mother who had no psychotic illness. This woman also smoked; her infant’s P1 S2:S1 ratio was 0.77. There were 35 depressed mothers and 4 depressed fathers, none paired with each other. These 4 depressed fathers had partners who did not smoke. The mean P1 S2:S1 ratio of their infants was similar to those whose parents had no risk factors (mean [SD] 0.44 [0.29]).

**Associations With Individual Response Amplitudes**

The S2:S1 ratio of P1 amplitudes was chosen for the primary analysis because this measure has been associated with the genetic transmission of schizophrenia.11 However, amplitudes of the P1 responses to each stimulus were also analyzed individually (table 2). There were no associations of any risk factor on the response to the first stimulus. Infants with parental illness, parental psychosis, or maternal depression had an elevated amplitude of the response to the second stimulus compared to the infants with no parental illness whose mothers did not smoke ($F_{1,146} = 7.57, P = .003$). Neither the association of maternal smoking nor its interaction with parental illness was significant.

**Discussion**

**Factors Associated With Neonatal Cerebral Inhibition and Risk for Mental Illnesses**

Diminished cerebral inhibition, as measured by the inhibition of the infant P1 in a paired auditory stimulus paradigm, was found in infants whose parents had psychotic illnesses compared with infants of healthy parents. An analogous phenotype in adults, diminished inhibition of the P50 auditory evoked response, has been previously characterized as an endophenotype of the transmission of one aspect of genetic risk for schizophrenia and bipolar disorder. The similar relation of cerebral inhibitory deficits to a history of parental psychosis in adulthood and in these infants suggests that an inhibitory physiological abnormality may be associated with future risk of illness. It thus appears that the initial neurobiological manifestation of the genetic transmission of risk may have occurred during prenatal brain development.

Other perinatal risk factors for schizophrenia also showed significant associations with deficits in cerebral inhibition in the infants. Maternal depression was associated with diminished infant P1 auditory evoked response inhibition in this study. It has been associated with increased risk for schizophrenia in the context of a family history of psychosis.7 Prenatal nicotine exposure was also found to be associated with diminished inhibition of P1, and it has been associated with increased risk for psychotic symptoms in adolescence.9 We did not have mothers with clinically detected infections, but maternal infection is also a risk factor for the later development of schizophrenia.8 The maternal cytokine response has been proposed as the mediator of the effect of infection based on animal models. It is possible that cytokines also are involved in the effects of maternal depression and other forms of maternal stress.32 Because all these risk factors occur with substantial frequency in the population, we considered all of them, except maternal infection, in this study.

The potentially toxic effects of maternal nicotine use are noteworthy. Nicotine concentration in the placenta during maternal smoking is estimated to be up to 15% higher than that of the mother, and in utero nicotine exposure has been demonstrated to affect fetal neuronal formation and differentiation, replication, and apoptosis.33,34 Prolonged exposure to nicotine profoundly desensitizes α7-nicotinic receptors and could prevent their critical role in assisting the development of cerebral inhibition by increasing the chloride gradient to change the effects of GABA from excitatory to inhibitory.35

Psychopathology in the offspring of mothers who smoke, including both schizophrenia and attention deficit disorder, has been previously observed.10 However, early neurobiological effects of maternal nicotine use have not been characterized until now. Although nicotine exposure during fetal brain development because of its use by the mother during pregnancy is a likely cause, the infants are also exposed to secondhand smoke after birth. Smokers also have lower levels of folic acid, which may also cause developmental abnormalities.36 Regardless, the profound effects of nicotine exposure through the mother are equivalent to and independent of the effects of parental psychosis and thus represent a significant neurotoxic effect, potentially equal to the effects of genetic risk for severe chronic mental illness at this early stage of development.

**Limitations in Assessment of the Parents and Offspring**

Limitations of the study are in the assessment of the parents and the infants. First, we did not attempt to differentiate between psychotic illnesses in the analyses of their infants’ electrophysiology. Psychotic parents often have mixed schizoaffective presentations during early parenthood. The genetic overlap between the psychoses is also considerable, and both affective and nonaffective psychoses have been associated with diminished auditory sensory inhibition.12,37 All the mothers received formal diagnostic interviews, but only 50% of the fathers
participated. Therefore, their diagnostic status is not as certain, and it is possible that there is some selection bias in which fathers participated based on their own mental illness. More precise assessment of maternal depression, particularly as it relates to timing and duration during pregnancy, is needed. The use of self-report by the mothers for their smoking behavior is an additional limitation. It is possible that some mothers failed to disclose their smoking behavior or did not adequately report nicotine consumption. Additionally, our sample size for this study was not adequate to allow analysis of effects of maternal medications during pregnancy and lactation.

Because the subjects of this study are neonates, the full phenotypic expression of the neurobiological effects of these genetic and environmental factors cannot be determined. Their continued assessment as their development continues will allow more extensive evaluation of whether this neurobiological problem persists into adulthood as brain function matures and to what extent it predicts the eventual emergence of severe psychiatric illness. The use of active sleep, the predominant state of consciousness in neonates and the only one in which they can comply with electrophysiological recording, raises issues about whether this state is developmentally stable during the first 6 weeks of life and whether findings in this state are comparable with those in the waking state in adults. Before commencing this study, we validated that the pathophysiological differences in cerebral inhibition observed in adults with schizophrenia were still present in REM sleep, the adult analog of infant active sleep. Although neonates are rapidly developing, sleep states remain immature for the first 6 months of life. In the present study, there were no effects of gestational age on the electrophysiological responses, probably because the time window in development was constrained to a 6-week interval.

An additional limitation rests in the small sample sizes for the groups, particularly when parental history, maternal smoking, and depression are considered as independent variables. Nonetheless, the sample of families without any known risk factors was large enough to permit assessment of significant associations of each of the risk factors on cerebral inhibition. Thus, this study contributes the first physiological demonstration in neonates of the effects of risk factors that are also established at the epidemiological level and demonstrates convergent effects on the development of cerebral inhibition.

Possible Neurobiological and Molecular Mechanisms

The P1 S2:S1 ratio is a noninvasive measure of cerebral inhibition that uses the classic paired stimulus neurophysiological strategy. However, this global strategy does not localize the inhibitory deficit to a particular brain structure or mechanism. Functional magnetic resonance imaging using a similar paired auditory stimulus paradigm in adults demonstrates a relationship of loss of P1 inhibition to hippocampal hyperactivity, a commonly observed pathophysiological feature of schizophrenia. Loss of hippocampal cholinergic innervation after fimbria-fornix pathway lesions or pharmacological blockade of α7-nicotinic receptors or null mutations of CHRNA7 all produce decreased inhibition in the rodent hippocampus. Thus, the elevated S2:S1 ratio found in both adults with schizophrenia and the offspring of psychotic parents may represent the loss of hippocampal inhibition. However, the neurobiological mechanisms of the loss of cerebral inhibition from transmission of genetic risk, nicotine exposure, or maternal depression remain to be more definitively established.

Although this study did not assess genetic risk per se, previous studies of cerebral inhibition implicate involvement of nicotinic receptors, with CHRNA7 being a possible candidate gene. Deletions of the region of chromosome 15 that contains CHRNA7 are associated with the de novo appearance of schizophrenia in some families. A number of other genes that have been found to be associated with schizophrenia are also involved in brain development. Neuregulin-1 (NRG1), eg, is associated with schizophrenia and is involved in the assembly of receptors during development, including the α7-nicotinic receptor. The interaction between these genes and environmental factors such as nicotine exposure and depression is undoubtedly complex.

Conclusion

Altered neurodevelopment as indicated by abnormal auditory evoked potentials in infants of parents with psychosis or with mothers with major depressive disorder or with prenatal exposure to nicotine indicates that pathophysiological processes related to severe mental illness are already manifest at birth and raises the possibility that this early stage of brain development may be a unique window for neurobiological interventions that can alter the risk for the later development of mental illness. This study contributes a putative physiological marker for several risk factors—parental history of psychosis indicative of a presumed genetic risk, maternal depression, and maternal nicotine abuse—that have been shown to influence the later development of psychosis in epidemiological studies. One value of a physiological biomarker is to identify neuronal mechanisms that are altered by these risk factors and that ultimately become part of the pathophysiology of psychosis later in development. The discussion above describes some of these possible mechanisms. In addition, the early detection of physiological changes may permit contemporaneous monitoring of efforts to mitigate the effects of these risk factors during the perinatal period, decades before effects on the later development of psychosis can be detected. For example, perinatal intervention with choline, which
activates $\alpha_7$-nicotinic receptors, normalizes cerebral inhibition in DBA/2 mice, an inbred strain with deficient inhibitory responses to repeated auditory stimuli related to genetic abnormalities in \textit{CHRNA7} similar to those observed in some persons with schizophrenia.\textsuperscript{20,46} This normalization of cerebral inhibition, based only on perinatal treatment, persists in adulthood. Similar perinatal interventions in humans for pregnancies and infants with risk factors for schizophrenia thus constitute a possible primary prevention for schizophrenia.\textsuperscript{47}

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