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Autism Prevalence Following Prenatal Exposure to Hurricanes and Tropical Storms in Louisiana

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Abstract Hurricanes and tropical storms served as natural experiments for investigating whether autism is associated with exposure to stressful events during sensitive periods of gestation. Weather service data identified severe storms in Louisiana from 1980 to 1995 and parishes hit by storm centers during this period. Autism prevalences in different cohorts were calculated using anonymous data on birth dates and parishes of children diagnosed with autism in the state mental health system, together with corresponding census data on all live births in Louisiana. Prevalence increased in dose-response fashion with severity of prenatal storm exposure, especially for cohorts exposed near the middle or end of gestation ($p < 0.001$). Results complement other evidence that factors disrupting development during sensitive gestational periods may contribute to autism.

Keywords Autism · Autistic Disorder · Pregnancy · Prenatal stress · Disasters · Natural experiment

Introduction

Autistic Disorder (AD) is a particularly devastating disorder for both patients and their families, yet its etiology is understood for only a small percentage of cases, and little is known about how or when etiologic factors act (Fombonne 2005). Twin and family studies have indicated the importance of genetic factors in AD, but environmental factors also appear to play a role (e.g., Folstein and Piven 1991; Muhle et al. 2004). Most AD cases do not fit a simple Mendelian pattern of inheritance. Carriers of susceptibility genes for non-Mendelian disorders often do not develop the disorders, and environmental factors may determine which gene carriers become ill (e.g., Smalley et al. 1988).

More investigation is therefore needed to elucidate environmental factors in AD; discovery of factors that could be modified and used for primary prevention would be particularly valuable. Several converging lines of research suggest that prenatal exposure to environmental hardships or stressful life events might be one such environmental factor. Prenatal exposure to stressful life events has been found to be associated with increased risk for several psychiatric disorders, such as schizophrenia and mood disorders (e.g., Huttunen and Niskanen 1978; Kinney 2001; Watson et al. 1999). Results from the following two studies have indicated this may be true for AD as well. Beversdorf et al. (2005) found that mothers of AD children reported significantly more stressful life events in their pregnancies with the AD children than did mothers of control children. Ward (1990) found that mothers of AD children were more likely than mothers of control children to report having experienced discord with family members when they were pregnant. A number of careful studies have found that rates of pre- and perinatal obstetric complications (OCs) are also significantly elevated in AD children compared with controls (e.g., Burd et al. 1999; Gillberg and Gillberg 1983; Glasson et al. 2004; Juul-Dam et al. 2001; Torrey et al. 1975).

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Research on animals (e.g., Schneider et al. 1999; Weinstock 1997) and humans (e.g., King and Laplante 2005) has shown that prenatal exposure to environmental stressors can produce postnatal behavioral abnormalities that resemble features associated with AD, including impaired social interaction, stereotyped behavior, cognitive and language deficits, and hypersensitivity to postnatal stress. This last effect is especially interesting because some evidence from early intervention studies in AD suggests that such hypersensitivity in infants may be a key factor increasing vulnerability to AD (Zelazo 2001).

To affect postnatal development, moreover, prenatal stress need *not* be chronic or extremely severe; animal experiments have shown lasting effects can be produced by relatively mild levels of stress (e.g., Clarke et al. 1996), or by injection of a synthetic stress hormone on a single day of gestation (e.g., Scheepens et al. 2003). Prenatal stress can affect postnatal outcomes through several mechanisms that disrupt brain development—e.g., by (a) impairing placental circulation, or (b) stimulating release of stress hormones that cross the placenta and alter the hypothalamic-pituitary-adrenal (HPA) axis, producing postnatal hypersensitivity to stress (Matthews 2000; Mulder et al. 2002). Perinatal OCs can also produce postnatal hypersensitivity (Brake et al. 1997) and increased social withdrawal and behavioral stereotypy (Laviola et al. 2004).

Theoretical and empirical considerations suggest that there may be two sensitive prenatal periods when stress exposure is especially likely to increase risk for AD. Extensive research on teratogenesis has shown that effects of a teratogen depend critically on the prenatal period when exposure occurs; effects of a teratogen are usually greatest if exposure occurs when a developmental process is occurring most rapidly. Prenatal development of the brain involves several different processes—such as cell proliferation, migration, differentiation, and synapse formation—with the activity of each process peaking at a different time. For example, in humans, neuronal migration peaks near the middle of gestation, whereas synapse formation peaks later, in the perinatal period. Thus, abnormal development of a given brain structure can result from teratogen exposure at more than one sensitive prenatal period. In the case of schizophrenia, in studies that could specify particularly well the time of exposure to a stressful life event (Huttunen and Niskanen 1978; Kinney 2001), the data pointed to two sensitive prenatal periods when exposure is especially likely to increase risk of illness: one period near mid-gestation, and a second in the several weeks just before birth.

In AD, evidence for significant associations with both prenatal and perinatal OCs also suggest two sensitive periods. Several studies found an association of AD with prenatal OCs, especially uterine bleeding (e.g., Juul-Dam et al. 2004; Gillberg and Gillberg 1983). Torrey et al. (1975) used detailed, prospectively collected, prenatal OC data and found a strong association of AD with bleeding near mid-gestation, especially in the fifth and sixth months of pregnancy, suggesting that these 2 months may comprise a sensitive period. A second sensitive period in AD, in the several weeks just before birth, is suggested by elevated rates of perinatal OCs in AD (Burd et al. 1999; Gillberg and Gillberg 1983; Glasson et al. 2004; Juul-Dam et al. 2001).

However, because of limitations in their research methods and designs, studies to date have not conclusively demonstrated that prenatal exposure to either stressful life events or OCs is etiologically significant in AD. The high reported rates of these pre- and perinatal problems might, for example, be (a) secondary (pleiotropic) effects of genes for AD, or (b) the result of unfavorable prenatal environments being correlated with adverse postnatal environments that help cause AD. Some studies may also have had (c) biases from retrospective maternal reports. More conclusive tests for prenatal environmental factors in AD—and of periods especially sensitive to such factors—are needed. A controlled experiment that randomly assigned pregnant women to high versus low-exposure to a stressful condition during different gestational periods would provide the most rigorous test, but this would be neither ethical nor practical.

An alternative approach is to take advantage of natural disasters, such as hurricanes, as "experiments of nature" that expose large numbers of pregnant women to a stressful event in an arbitrary, essentially random manner. This approach approximates the design of a controlled scientific experiment, because the level of exposure to the stressful circumstance is likely to be independent of factors such as parental genotype, socioeconomic status or personality, which may be confounded with other types of stressful life events or with OCs. Moreover, natural disasters occur at specific times and places that are noted in public records, aiding investigation of how the timing of prenatal exposure may affect the risk for disorders. Several previous studies using this approach found significant associations between prenatal exposure to disasters during certain periods of gestation and increased risk for adult psychiatric disorders (Kinney 2001; Watson et al. 1999) or children's behavioral problems, including poorer cognitive and language development and more stereotyped behavior (King and Laplante 2005).

Methods

The present study utilized a series of natural disasters to test the hypotheses that (a) risk for AD increases in a dose-response manner with the severity of prenatal exposure to

disasters, and (b) there are sensitive periods of gestation when such exposure is more likely to increase risk for AD. The disasters used were severe storms that hit Louisiana from 1980 to 1995.

Louisiana's Department of Health and Hospitals (DHH) supplied an anonymous limited data set on the birth dates, birth parishes (counties), and gender of all individuals seen in the state health system since 1990 who had a diagnosis of AD based on *DSM-III-R* or, in most cases, *DSM-IV* criteria (American Psychiatric Association 1994). AD cases were excluded if genetic syndromes associated with AD were also present (e.g., fragile X syndrome, tuberous sclerosis). An anonymous limited data set on the gender and birth parish of all children born in Louisiana during the time periods under investigation was obtained from the National Center for Health Statistics (NCHS) in Hyattsville, Maryland. These data were used to calculate the prevalence of AD (i.e., the number of AD cases per 10,000 births in the general population of the respective parishes and time period) for each cohort of interest. To investigate how timing of storm exposure affected prevalence, the normal 40-week term of gestation was divided into five equal periods, each period being 8 weeks (or two four-week "months"). Although the use of shorter gestational periods would have been desirable, it would have yielded too few AD cases in each period to provide adequate statistical power. Moreover, data on individual gestation lengths were not available, so 40-week gestations were assumed when estimating gestational age during storms.

To identify the severe storms, we used data from the National Weather Service on all hurricanes, tropical storms, or floods that struck Louisiana from 1980 to 1995, including the storms' dates, tracks, and degree of destructiveness. Storms before 1996 were used in order to increase the likelihood that children exposed to storms would be old enough to have appeared in the state mental health system by the time of our study. Ten such disasters had a particularly severe impact on Louisiana during this 16-year period: Tropical Storm Chris (1982); Hurricanes Danny, Elena, and Juan (1985); an unnamed tropical storm (1987); Tropical Storm Beryl and Hurricane Florence (1988); Hurricane Andrew (1992); and Hurricane Opal and an unnamed storm that caused particularly severe flooding (1995). Based on the NCHS census data, a total of 320,686 children would have been in utero and in Louisiana when any of these ten storms struck. Of these children, 167 received a diagnosis of AD according to Louisiana DHH records, yielding an overall AD prevalence of 5.21 per 10,000 live births (CL = 4.42–6.00). To test the study's hypotheses, several analyses were conducted comparing the AD prevalence among different cohorts of children within this total sample.

To rank the severity of prenatal storm exposure that different cohorts of children had experienced, two factors were used: (a) the intensity of a storm's impact on a parish, and (b) how vulnerable to storms' effects residents would tend to be if a storm hit their parish. National Weather Service maps of storm tracks were used to identify the parishes that were hit by the centers of each storm, and thus were likely to have experienced the most intense effects of the storm. Expectant mothers in Orleans Parish were particularly likely to be vulnerable to storm effects because, as the effects of Hurricane Katrina in 2005 demonstrated, New Orleans' population is particularly vulnerable to the effects of storms because much of the city is below sea level and subject to severe flooding (the boundaries of Orleans Parish and New Orleans are identical). Moreover, a relatively high proportion of New Orleans residents have incomes near or below the poverty line and tended to have fewer resources available to cope with storms' effects. The combination of these two storm factors—intensity and vulnerability—were used to establish the severity of storm exposure in different cohorts.

The analysis of the data involved several steps. First, we estimated the prevalence of AD in each storm exposure group, considered separately, using point estimates and 95% confidence intervals. Second, a test of the hypothesized trend for prevalence to increase across groups with increasing severity of storm exposure was performed with the Cochran–Armitage trend test (Armitage 1955; Cochran 1954; Fleiss et al. 2003). Third, because, as research discussed in the introduction suggests, there may be sensitive periods when prenatal stress will have greater effects on AD risk, we conducted an overall chi-square test of whether AD prevalence differed significantly among groups exposed to storms at different gestational periods. Fourth, when this overall test was significant, pairwise tests for differences in prevalence between gestational period groups were conducted with Fisher's exact test, using a significance criterion set at a two-tailed $\alpha = 0.05$, and a Bonferonni adjustment to account for multiple possible comparisons among pairs of groups. Fifth, multiple logistic regression analysis was used to examine the association between exposure, gestational period and the interaction between exposure and gestational period on AD prevalence. Sixth, gender differences in prevalence and their interaction with storm exposure were examined. All data analyses were performed using SAS statistical software, Version 9.1 (SAS Institute, Cary, NC, USA). All prevalence rates are presented here as the number of AD cases per 10,000 live births in the corresponding cohort. All confidence limits (CL) of prevalences are at 95%.

Results

AD Prevalence Increased with the Severity of Prenatal Storm Exposure

The first analysis examined whether the prevalence of AD increased with the severity of prenatal storm exposure. For this analysis, cohorts were grouped by severity of storm exposure. The high-exposure cohort had both exposure severity factors—i.e., was in utero (a) in New Orleans when (b) hurricane centers passed directly through the city. The intermediate-exposure cohort had one of the two factors (i.e., children in the cohort were either born in New Orleans, or born in a parish that was hit by a storm center, but not both). The control, or low-exposure, cohort consisted of children who were also born (a) in Louisiana and (b) during the same time periods as the children in the high and intermediate-exposure cohorts, but had neither of the storm severity exposure factors (i.e., they were born in Louisiana parishes other than Orleans, and they also had no prenatal exposure to a storm center). As hypothesized—see Table 1—the prevalence of AD increased in dose-response fashion with the severity of storm exposure; this trend was significant (Cochran–Armitage Trend Test, $Z = 3.31$, two-sided $p < 0.001$).

AD Prevalence Depended on Prenatal Period of Storm Exposure

A second analysis examined whether AD prevalence was associated with the particular gestational periods when storm exposure occurred. The initial examination of this issue encompassed all children born in New Orleans with prenatal exposure to storms. Table 2 shows that AD prevalence varied with storm exposure in the five different 8-week gestational periods. As Fig. 1 shows, AD prevalence differed greatly by gestational period at the time of storm exposure, χ^2 ($df = 4$, $N = 55{,}566$) = 21.89, $p = 0.0002$. The highest AD prevalence rates were for cohorts of children exposed to storms near the middle (months 5, 6) or the end (months 9, 10) of gestation. For cohorts exposed in these four more sensitive months, the combined AD prevalence was 14.15 per 10,000 (CL: 9.32–18.97), whereas for cohorts exposed in the other six, less sensitive, months of gestation the combined AD prevalence was only 3.72 (CL: 1.62–5.83). The difference in prevalence between the more- versus less-sensitive periods was significant (OR: 3.83, CL: 1.98–7.42, $p < 0.00003$). The difference in prevalence between these exposure periods remained significant after a Bonferroni adjustment for all possible pairwise comparisons of groups (two-tailed Fisher exact test, $p < 0.003$). In contrast, the prevalence among the children exposed to storms during the period comprising months 5 and 6 did not differ sig-

Table 2 Prevalence of Autistic Disorder (*AD*) in Orleans parish varies with gestational age at time of storm exposure

Gestational age during storm	AD cases/ cohort	AD prevalence per 10,000 births	95% CL of prevalence
Months 1–2	3/10,241	2.93	0.00–6.24
Months 3–4	5/10,492	4.77	0.59–8.94
Months 5–6	20/11,272	17.74	9.97–25.51
Months 7–8	4/11,504	3.48	0.07–6.88
Months 9–10	13/12,057	10.78	4.92–16.64

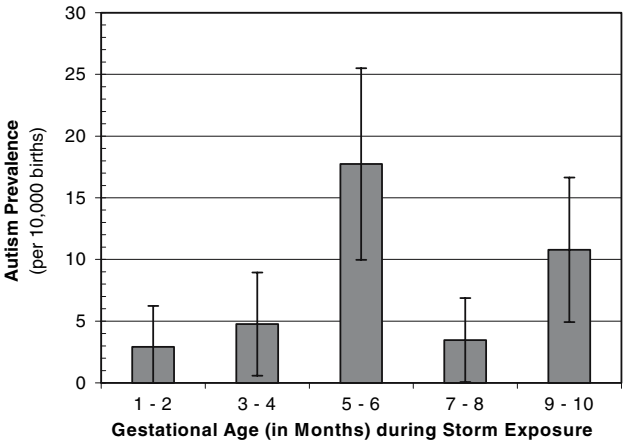

Fig. 1 Prevalence of Autistic Disorder (*AD*) among children born in Orleans parish, by gestational age at time of storm exposure.*Note*: Error brackets represent the 95% confidence limits on prevalence

Table 1 Prevalence of Autistic Disorder (*AD*) increases with severity of prenatal storm exposure, defined by factors of storm intensity and storm vulnerability

Severity of storm exposure	AD cases/cohort	AD prevalence per 10,000 births	95% CL of prevalence
High-exposure (both severity factors present)	12/9,003	13.32	5.8–20.9
Intermediate-exposure (only one factor present)	58/95,651	6.06	4.5–7.6
Control/low-exposure (neither factor present)	97/216,032	4.49	3.6–5.4

The storm intensity factor was present if children were exposed to a storm's center. The storm vulnerability factor was present if children were exposed in New Orleans

nificantly from that of children exposed during the period comprising months 9 and 10. Nor did the prevalence differ significantly among the children exposed in the three less sensitive periods of gestation.

A parallel pattern was found for children from Louisiana parishes other than Orleans who were in utero when storm centers passed directly through those parishes. For these children as well, AD prevalence was significantly higher if storm exposure occurred in months 5–6 or 9–10 (prevalence of 7.67; 16/20,852) than in other months of gestation (prevalence of 3.19; 9/28,236; $p < 0.04$, two-tailed exact test of difference in prevalence; odds ratio = 2.41; CL: 1.06–5.45).

Interaction of Severity and Timing of Storm Exposure on AD Prevalence

The next analysis examined whether these two predictor variables—severity of exposure and gestational period of exposure—interacted significantly. A multiple logistic regression analysis indicated that the combination of exposure severity and timing was significantly associated with AD prevalence: for the Wald test, $\chi^2(df = 5, N = 320{,}686) = 44.57$, $p < 0.0001$. The interaction of exposure severity with timing of exposure was also significant: Wald χ^2 ($df = 2$, $N = 320{,}686$) = 18.91, $p < 0.0001$.

As shown in Table 3 and Fig. 2, AD prevalence increased markedly with the severity of storm exposure if the exposure occurred during the *more* sensitive gestational periods (Cochran–Armitage Trend Test, $Z = 6.01$, two-sided $p < 0.0001$). AD prevalence was especially high (26.6) for New Orleans children who were in the more sensitive periods of their gestation when the center of severe hurricanes passed directly through New Orleans. In contrast, if storm exposure occurred during one of the *less* sensitive gestational periods, prevalence was consistently relatively low, regardless of the severity of exposure (Cochran–Armitage Trend Test, $Z = -1.36$, p not significant).

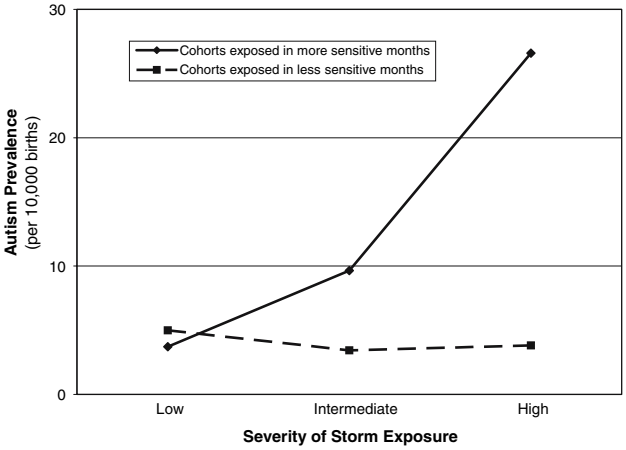

Fig. 2 The relation of AD prevalence to severity of storm exposure depends upon the gestational period when exposure occurs

Gender Differences in Prevalence

In accord with most studies of AD, prevalence was higher for males (7.84; 128 cases/163,300 male births; CL 6.48–9.20) than for females (2.84; 39 cases/157,386 female births; CL 1.70–3.26); the odds ratio for males to females was 3.16 (CL: 2.21–4.53; $p < 0.0001$, two-tailed exact test). The effect of storm exposure severity tended to be stronger among males than females, but this was not statistically significant.

Discussion

Autistic Disorder prevalence in Louisiana children increased significantly with the severity of prenatal storm exposure. This increase in prevalence with severity of exposure was concentrated in children who were exposed during particular prenatal periods: the months near the middle or end of gestation. These results complement other research evidence that prenatal exposure to stressful events,

Table 3 Prevalence of Autistic Disorder (*AD*), by timing and severity of storm exposure

Timing and severity of storm exposure	AD cases/cohort	AD prevalence per 10,000 births	95% CL of prevalence
More sensitive months (5–6, 9–10)			
High-exposure (both factors)	10/3,761	26.59	10.12–43.05
Intermediate-exposure (one factor)	39/40,420	9.65	6.62–12.68
Low-exposure (neither factor)	32/85,968	3.72	2.43–5.01
Less sensitive months (1–4, 7–8)			
High-exposure (both factors)	2/5,242	3.82	0–9.10
Intermediate-exposure (one factor)	19/55,231	3.44	1.89–4.99
Low-exposure (neither factor)	65/130,064	5.00	3.78–6.21

including natural disasters, is associated with adverse outcomes in children, including behavioral problems (e.g., Glover 1997; King and Laplante 2005; Watson et al. 1999).

The study's results raise the intriguing possibility that exposure to environmental stress or hardship during sensitive periods of gestation not only may increase risk for AD, but may also help to explain several behavioral features of AD. In studies of both humans and laboratory animals, prenatal exposure to maternal stress increased rates of key behavioral problems resembling those seen in AD, such as abnormal social behavior (e.g., Clarke et al. 1996). Prenatal stress has particularly strong effects on systems that mediate response to stress (e.g., Weinstock 1997; Matthews 2000), producing postnatal hypersensitivity to stress, something also found in AD children (e.g., Corbett et al. 2006).

Our study's results also complement earlier research in suggesting that prenatal stress could be a common factor that helps to mediate the association of AD with several other previously identified risk factors. If prenatal stress contributes to AD, this could help explain why: (a) OCs increase the risk for AD (because maternal stress can cause OCs; see Kennell et al. 1991); (b) AD is three to four times more common in males than females (because males tend be more vulnerable to prenatal stressors; see Clarke et al. 1996); and (c) why abnormalities in brain growth and in the morphology of certain brain regions (e.g., Courchesne and Pierce 2005) are found with AD (because prenatal stress can disrupt brain development, and in animal experiments it has produced abnormalities in some of those same brain regions—e.g., Ahlbom et al. 2000).

The strengths of the present study's design complement those of studies cited earlier that also found significant associations of AD risk with prenatal exposure to stressful life events or OCs. Thus potential artifacts (such as possibly biased maternal reports, or confounding of prenatal factors with parental genotypes), which might conceivably have explained the association of prenatal factors with AD in those previous studies, are unlikely to have done so in the present study because of its research design using natural experiments. Conversely, although the present study had limited data on aspects of individual mothers' pregnancies, such as length of gestation or specific details of life event experiences, those data *were* available in the other studies that found prenatal stress was associated with AD risk. That severe storm exposure is likely to have increased mean levels of distress in expectant mothers in our study is supported by other research which found that similar natural disasters significantly increased individuals' levels of psychological distress and HPA arousal (e.g., Anisman et al. 2001). Moreover, women, particularly mothers of young children, are especially likely to suffer distress from disaster exposure; e.g., a review of studies of psychological effects of disasters (Norris et al. 2001) found that, in 42 of 45 samples studied, women or girls were affected more adversely than men or boys.

New studies are needed to investigate whether our findings replicate in other samples and disasters. Of particular interest is whether more detailed data on severity and timing of prenatal disaster exposure would identify even more narrowly defined sensitive periods and stronger associations between AD risk and exposure to stressful events during those periods.

It should be emphasized that the present study is only an initial step toward relating prenatal stress to risk for AD. As noted earlier, prenatal stress has also been found to be associated with increased risk for several other psychiatric disorders, including schizophrenia and depression. Thus, a key question for future research is why prenatal exposure results in AD in some cases, other mental disorders in other cases, and healthy outcomes in still other individuals. There are a number of mechanisms that might explain these different outcomes. Important factors that mediate the effect of prenatal stress, and that contribute to different behavioral outcomes, are likely to include the timing and severity of exposure to a stressful event. Outcomes may depend on the specific stage of brain development that is occurring at the time of exposure. For example, different psychiatric disorders may tend to involve abnormalities in different brain structures that have somewhat different developmental timetables, so that the gestational periods when development of those structures is most sensitive to the teratogenic effects of stress are likely to differ as well.

Even when the timing and severity of prenatal exposure are the same, behavioral outcomes may still differ significantly, because the effect of prenatal exposure to a stressful event on development will also depend on other factors, such as the physiological response of the mother and fetus to the event. A mother's response to a stressful event will be influenced by multiple factors that could be investigated in future studies. These factors include (a) the social resources that the mother has to help cope with the event, (b) the mother's temperament, including her emotional reactivity to stressful situations, (c) individual differences in the levels of stress-related hormones such as cortisol that are released into the maternal bloodstream in response to the stressful event, and (d) the effectiveness of the placenta in buffering the fetus against exposure to harmful levels of cortisol. Of note in this regard are reports that mothers of AD children are more likely to (a) report having had family conflicts when pregnant (Ward 1990), (b) have a history of disorders associated with high reactivity to stress (Piven and Palmer 1999), and (c) have had obstetrical complications involving the placenta during their pregnancies or labor with AD children (Glasson et al. 2004).

Given the evidence for significant heritability of AD, as well as many other psychiatric disorders, whether prenatal stress results in a particular disorder is also likely to be influenced by how stressful stimuli interact with an individual's genotype. One possible mechanism for such interactions would be epigenetic effects of stress on the expression of genes that influence the functioning of the HPA axis; animal experiments have demonstrated how early environmental experience can influence epigenetic programming of the response to stress (Fish et al. 2004).

To investigate these issues, further research is required that includes additional measures and comparison or control groups not available in the present study. For example, studies are needed that apply a research design similar to that used in the present study, but go further to examine how the timing and severity of exposure to the same stressful event, such as a natural disaster, are related to risk not just for AD, but also for other disorders, such as ADHD, schizophrenia, and depression. A complementary approach would involve comparing groups with AD to comparison groups that were demographically matched, and had the same prenatal exposure, but that either (a) developed other mental disorders or (b) had healthy outcomes, in order to examine how groups with different outcomes differ on potential moderating variables. Particularly interesting candidates for moderating variables would include the personality and social environment of the subjects' mothers, and the subjects' own genotypes—e.g., genes known to strongly influence prenatal brain development and/or the activity of stress-response systems, both pre- and postnatally.

Our results suggest the interesting possibility that efforts to protect expectant mothers from stress might be useful in primary prevention of AD. While most individuals with AD may not have had prenatal exposure to disasters, many *will* have had prenatal exposure to other stressful events, as Beversdorf et al. (2005) found. Protecting expectant mothers from stressful circumstances could also provide a way to use *other*, less malleable, AD risk factors, such as genetic susceptibility (e.g., Campbell et al. 2006), for primary prevention. That is, these other risk factors could help identify pregnancies at particularly high risk for AD, so that they could then be targeted by special efforts to optimize prenatal care and reduce maternal stress.

Finally, because prenatal stress tends to produce postnatal hypersensitivity to stress, our results complement evidence that AD children show such hypersensitivity (Corbett et al. 2006), which some research suggests may be a core vulnerability predisposing to AD; consequently early interventions to increase stress tolerance could be a promising approach to treating children who have, or are at high risk for, AD (Zelazo 2001). Thus, several considerations indicate that the possible etiologic role of pre- and perinatal stressors in AD deserves more investigation.

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