Prenatal Stress and Risk for Autism

Dennis K. Kinney, Ph.D.a,b,* Kerim M. Munir, M.D., M.P.H., D.Sc.b,c, David J. Crowleya, and Andrea M. Millera

aMailman Research Center, McLean Hospital, 115 Mill St., Belmont, MA, 02478, USA
bDepartment of Psychiatry, Harvard Medical School, 25 Shattuck St., Boston, MA, 02115, USA
cDivision of Developmental Medicine and Department of Psychiatry, Children’s Hospital Boston, 300 Longwood Ave., Boston, MA, 02115, USA

Abstract

This paper reviews several converging lines of research that suggest that prenatal exposure to environmental stress may increase risk for Autistic Disorder (AD). We first discuss studies finding that prenatal exposure to stressful life events is associated with significantly increased risk of AD, as well as other disorders, such as schizophrenia and depression. We then review evidence from animal and human studies that prenatal stress can produce both (a) abnormal postnatal behaviors that resemble the defining symptoms of AD, and (b) other abnormalities that have elevated rates in AD, such as learning deficits, seizure disorders, perinatal complications, immunologic and neuroinflammatory anomalies, and low postnatal tolerance for stress. We explain why an etiologic role for prenatal stress is compatible with genetic factors in AD, and describe how stress can disrupt fetal brain development. Finally, we discuss implications for understanding underlying processes in AD, including potential gene-environment interactions, and developing new therapies and early prevention programs.

Keywords

Prenatal stress; autism; epidemiology; risk factors; pregnancy; human and animal research; obstetric complications; natural experiment

1. The Symptoms, Prevalence, and Costs of Autism

Autistic Disorder (AD) is a particularly severe neurodevelopmental disorder, with great costs for society as well as for patients and their families. The most widely used diagnostic criteria for AD are those described in the revised text edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) of the American Psychiatric Association (APA, 2000). Briefly stated, those criteria involve a) qualitative impairment of reciprocal social interactions, b) marked impairment in the development of communication, and c) severely restricted, stereotyped, and repetitive patterns of interests and behaviors. There must also be delayed or abnormal functioning before age 3 year in one of more of the areas of social interaction,
language, or symbolic and imaginative play. Most individuals with AD have significant life-long impairments in social and language functioning, and only a small percentage of individuals with AD are able to live and work independently as adults. AD is four to five times more prevalent in males than females.

AD usually involves significant disabilities for those affected, and significant distress for both patients and their families. A British study estimated that the lifetime economic cost for an individual with AD exceeds $2 million (Jarbrink & Knapp, 2001), while a Swedish study conservatively estimated the societal cost per child for schooling and other community support at more than $50,000 per year, not counting an average of approximately 1000 hours per year that parents spend supporting and caring for their autistic child (Jarbrink, 2007).

Recent research indicates that the prevalence of AD and related autism spectrum disorders is much greater now than was recognized even a decade ago and may be as high as one child in every 150 (Centers for Disease Control, 2007). The etiology of AD is understood in only a small percentage of cases, however, and little is known as to how or when during development etiologic factors act in AD (Fombonne, 2005).

2. Overview of Genetic and Environmental Factors in Autism

Although the importance of genetic factors in AD is strongly suggested by data from twin, family, and genetic association studies (e.g., Campbell et al., 2006; Folstein & Piven, 1991; Muhle et al., 2004), the same studies also indicate that environmental factors play a significant role. The much higher concordance rates in monozygotic (MZ) compared to dizygotic (DZ) twin pairs do point to a high heritability in AD, but these rates also suggest that exposure to environmental modifiers may contribute to variable expression of autism-related traits (Muhle et al., 2004). Freitag (2007) noted that the pairwise concordance rates for AD in the four twin studies of AD were much higher for MZ twins (concordance ranged from 36–96% in the four studies) than for same-sex DZ twins (0–30% concordance range). It should be kept in mind, however, that some aspects of the prenatal, as well as the postnatal, environment tend to be more similar for MZ than DZ co-twins; for example, about 75% of MZ, but less than 10% of DZ, twins appear to share vascular connections in utero (Hall, 2007).

Moreover, gene-environment interactions are one process that can produce much higher concordance in MZ than DZ twins. For example, if a disorder requires an environmental trigger acting on an unusual ensemble of several susceptibility alleles, then environmental exposure leading to illness in one twin will also likely lead to illness in an MZ co-twin (who also inherits that ensemble of genes), whereas a DZ co-twin will rarely inherit the genetic ensemble required for the illness. Thus twin data do not exclude an etiologic role for environmental factors in AD; indeed, the only unequivocal conclusion to be drawn from the twin data is that environmental influences must be significant in some AD cases, as MZ concordance is less than 100%.

In addition, most AD cases do not follow a Mendelian pattern of inheritance, and in non-Mendelian disorders, environmental factors often determine whether individuals who carry susceptibility genes become ill (Smalley et al., 1988). Recent research in both animals and humans has discovered a number of gene-environment interactions in which exposure to a pre- or postnatal environmental pathogen causes a behavioral disorder only if an exposed individual carries a specific genetic variant (Casi & Moffitt, 2006; Rutter et al., 2006). In one type of gene-environment interaction (Meaney & Szyf, 2005), discussed later, perinatal stress has long-lasting effects on expression of genes that modulate postnatal responses to stressful events.
3. The Importance of Identifying Preventable Environmental Causes of Autism

Because AD is so devastating and there is, with rare exception, no established method for preventing AD, research is urgently needed to identify potential environmental factors that contribute to AD. Identification of environmental factors that can be avoided, prevented, or ameliorated by programs of primary prevention is therefore especially important.

In this paper, we review several complementary lines of research that suggest that one environmental factor that increases risk for AD is prenatal exposure to stress, in the form of stressful life events or environmental hardships that distress an expectant mother. Whether prenatal exposure to stress could be etiologically significant in AD is an issue that has received little attention, but could be important for clinical as well as scientific reasons. We first review evidence that prenatal exposure to stressful life events is associated with increased risk of developing several psychiatric disorders, including AD. We then review evidence from research on animals and humans that prenatal stress can produce a variety of adverse effects on subsequent postnatal behavior, including behaviors that resemble key symptoms of AD, as well as cognitive, neurological, and immunologic abnormalities associated with AD. We discuss different physiological mechanisms by which prenatal stress can affect fetal development and postnatal behavior. We also point out how prenatal stress may help to explain why certain factors, such as gender, obstetric complications (OCs), and parental infertility, are associated with increased risk for AD.

If prenatal stress is in fact etiologically significant in AD, this would have important clinical implications, and we discuss some of these in a later section on Implications for Prevention and Treatment. For example, efforts to prevent or reduce stress in pregnancies at high risk of AD (e.g., because of factors such as genetic profiles or family history) could be used in programs for primary prevention of AD. Such efforts could also complement ongoing research on other AD risk factors, either by preventing certain factors, as in the case of OCs, or by providing a way for prevention programs to use other factors, such as family history.

4. Prenatal Stress and Increased Risk of AD

Two retrospective studies have found that prenatal exposure to stressful events is associated with increased risk of AD. Ward (1990) compared data from prenatal records of 59 mothers of AD children to records of a matched sample of 59 mothers of healthy children. He found that the mothers of AD children reported having experienced significantly more family discord during the pregnancies with the AD children: 19 of the mothers of AD children, but only 2 of the control mothers, experienced discord during their pregnancies with their children \( (p < 0.05) \).

In a similar study, Beversdorf et al. (2005) found that 188 mothers of AD children reported having experienced significantly more stressful life events—such as job loss or death of husband—during their pregnancies (44.7 events per 100 responses) than did 202 mothers of typically developing children (25.9 events per 100 responses; \( p = 0.0007 \)). The study also included a comparison group of 92 mothers of children with Down syndrome; the average number of stressful events reported by these mothers (26.1) was almost identical to that of control mothers. The authors report that the child’s age at the time the mothers reported on stressful life events they experienced during their pregnancies, which might potentially have affected mothers’ recall accuracy, was not, in fact, significantly correlated with the number of stressful life events reported.

These two studies are noteworthy, but they had important limitations. For example, the higher average number of stressful events that mothers reported having experienced during their pregnancies with AD children (Beversdorf et al., 2005) could potentially have been due to (a)
biased maternal retrospective reports, (b) a general tendency for mothers of AD children to experience more stressful life events, regardless of whether they are pregnant, or (c) a tendency for those mothers to experience more stressful life events in all of their pregnancies, regardless of whether their children develop AD. Another difficulty with the research design used by Ward (1990) and Beversdorf et al. (2005) is that it cannot exclude the possibility that the elevated levels of maternal stress during pregnancy might be correlated with other etiologic factors, such as adverse postnatal environments and/or parental genotypes, which might actually be the important contributors to the development of AD in these children. (For example, mothers who experience more marital or financial problems while pregnant might continue to experience more of these problems after their children are born.) The stressors used in these studies also make it difficult to identify possible critical periods of prenatal development when exposure to stressors might be most likely to increase risk for AD. Many stressful life events do not have a precise time of occurrence, and even those that do, such as divorce or loss of job, may also have been preceded or followed by stressful periods associated with the event. There is a need for new research using designs less subject to these problems.

The most powerful tool for testing whether prenatal stress is a causal factor in a disorder such as AD would be a scientific experiment in which pregnant women were randomly assigned to conditions of high or low exposure to stress. Obviously, this would be neither ethical nor feasible. There is an alternative research strategy, however, that can help to overcome these key limitations of previous research on AD: using natural disasters as “experiments of nature” to investigate these questions in a way that is ethical, feasible and economical. Unlike most stressful events, disasters are likely to be independent of subjects’ genotypes, socioeconomic status, personality, or other confounding characteristics; disasters tend to strike in a manner that resembles the random assignment of subjects in a scientific experiment. Moreover, because the chronology and location of natural disasters are often available in public records, they can provide data on prenatal stressors that are not dependent on retrospective recall. Disasters can also be linked more precisely than most stressful events to specific periods of gestation when exposure to environmental stressors may be most likely to lead to a disorder.

Kinney et al. (2008) used hurricanes and severe tropical storms as natural experiments to investigate whether AD is associated with exposure to stressful events during sensitive periods of gestation. The most destructive storms affecting Louisiana between 1980 and 1996 were identified using National Weather Service data. To measure the effect of exposure, AD prevalence rates in different cohorts were calculated using anonymous limited datasets on birth dates and birth parishes (counties) of children diagnosed with AD in the Louisiana state mental health system, together with corresponding census data on all live births for the same periods and parishes. The severity of prenatal storm exposure experienced by different cohorts of children was ranked using two storm factors: (a) the intensity of a storm’s impact on a parish, and (b) the vulnerability of the residents of a parish to a storm’s effects. Weather Service maps of storm tracks identified the parishes that were hit by a storm’s center and thus were likely to have experienced the most intense effects of the storm. Mothers in Orleans Parish (which is geographically identical to New Orleans) were particularly likely to be vulnerable to storms’ effects because, as seen with Hurricane Katrina in 2005, much of New Orleans is below sea level and subject to severe flooding. Moreover, a relatively high proportion of New Orleans residents is near or below the poverty line, and has fewer resources to cope with storms’ effects.

AD prevalence was found to increase significantly, in a dose-response fashion, with the severity of prenatal storm exposure, from (a) the control cohort that had no exposure to either storm factor (prevalence of 4.49 AD cases per 10,000 births), to (b) the cohort exposed to one or the other storm factor (AD prevalence of 6.06), to (c) the cohort exposed to both storm factors (prevalence of 13.32). The increase in AD risk with storm exposure was particularly large for children who had been exposed to storms in specific periods near the middle and end of
gestation. Children who had been exposed to storms during gestation months 5–6 or 9–10 had a 3.83 times greater risk of developing AD than children who had been exposed to the same storms, in the same place, but during other months of gestation ($p < 0.001$).

These results complement evidence from research described later, which indicate that pregnancy and birth complications are associated with increased risk for AD, particularly if the complications occur either in a period of several weeks near the middle of gestation or during the several weeks just before birth. In the study by Beversdorf et al. (2005), mothers of AD children reported having experienced more stressful life events in the last several months of pregnancy than in the first three months. However, all studies to date on prenatal stress and AD had limits to their methods; for example, none obtained data on either the AD children’s siblings or factors that may influence an individual mother’s responses to stressful life events. In the Kinney et al. (2008) study, it was not possible to ask individual mothers about personal storm-related hardships, their social and financial resources for coping with their hardships, or other possible teratogens such as toxins to which they might have been exposed as a result of the storm. These variables are likely to influence the physiological effects of a storm experience on a mother and her fetus. Moreover, because the study involved children with AD who had been seen in the state health system, children with AD who were treated privately would have been missed. However, any incompleteness in ascertainment of AD cases is unlikely to account for the study’s key findings, which involved comparisons of cohorts of children who were born in the same parishes and ascertained in the same manner.

If prenatal stress contributes to AD, one might expect that risk for AD would be very high in cohorts exposed to catastrophes such as earthquakes and tsunamis, particularly in the developing world, where people typically have less access to social and medical support in coping with such disasters. Unfortunately, there have been few studies on the prevalence of AD in developing countries, and no studies there on the effects of prenatal disaster exposure on risk for AD. Such studies are needed, though the logistics of such studies may prove difficult, particularly in developing countries that lack the mental health treatment and record-keeping systems to aid in ascertaining AD cases and estimating prevalence rates.

In summary, two different types of studies, using complementary research designs, have found significant associations between prenatal stress and increased risk for AD. Both types of studies also found evidence for vulnerable periods of gestation when exposure to maternal stressors was more strongly associated with risk for AD. These studies raise the question of whether an etiologic role for prenatal stress is consistent with what is known from other types of research regarding the effects of prenatal stress on postnatal development.

### 5. Research on Related Effects of Prenatal Stress

The existing evidence for significant effects of prenatal stress on postnatal behavior is robust. There are more than 100 experiments published in the scientific literature on the effects of prenatal stress in laboratory animals. There are also several dozen studies of humans, including several involving natural experiments. While an exhaustive review of all these studies is beyond the scope of this paper, several important and well-established general principles that are particularly pertinent to a possible role of prenatal stress in AD are described below.

#### 5.1 Different Types of Prenatal Stressors Can Affect Postnatal Development

One important discovery is that effects of prenatal stress on postnatal behavior are found for many different species and types of stress. Significant effects of prenatal stress have been found in a variety of mammalian species, including rodents and non-human primates, as well as in humans. Moreover, in studies of both humans and animals, many different types of prenatal stressors were found to have significant effects on postnatal behavior. Weinstock (2002), for
example, noted that procedures used to induce stress in pregnant rats have included saline injections, physical restraint, exposure to loud noises, foot-shocks, overcrowding, and immersion in cold water. The effects of exposure to prenatal stress on postnatal behavior have also been produced by exposing pregnant monkeys and rodents to stress hormones such as glucocorticoids (GCs) (Matthews, 2000; Scheepens et al., 2003). In the offspring of these pregnant animals, significant changes have been found in both behavior and regulation of the hypothalamic-pituitary-adrenal (HPA) axis, regardless of the specific prenatal stressor used.

In humans as well, significant effects on postnatal behavior have been found for prenatal exposure to many different types of maternal stress or anxiety. In several studies described elsewhere in this paper, prenatal exposure to natural disasters significantly increased the risk for a variety of behavioral disorders. These disasters tend to expose people in an arbitrary manner that approximates the random assignment of a true experiment. As with the true experiments with animals, an important advantage of these natural experiments is that the research design makes it more likely that an association of prenatal stress with postnatal behavior reflects a causal effect of the prenatal stress. However, a question posed by these laboratory and natural experiments is whether results can be extrapolated to the effects of more common, and less severe, life events that pregnant women experience (e.g., marital or employment problems).

It is noteworthy, therefore, that many different studies with humans have found significant associations between behavioral problems and prenatal exposure to more common life events or to reports of maternal anxiety. In these studies, the measures of maternal stress are more representative of the kinds of stresses to which children are likely to be exposed prenatally. One limitation of these latter studies, however, is that the measures of stress are less likely than in experimental studies to be independent of other variables, such as parental genotypes or socioeconomic status, that might potentially contribute to AD. The duration of the stressful event is also less likely to be less well defined than in laboratory or natural experiments.

Because each type of study has strengths and weaknesses, the case for a causal effect of prenatal stress on a particular kind of abnormal outcome is much stronger if prenatal stress has been associated with the outcome in a variety of studies that use different research designs and measures of stress, so that an association can not be dismissed simply as an artifact of a particular methodological weakness. Therefore, in reviewing evidence for possible effects of prenatal stress on a type of behavior, we have tried to identify whether associations between prenatal stress and a particular postnatal outcome have been reported in research using different designs, and in animal as well as human subjects.

Another important finding from experiments with laboratory animals is that prenatal stress does not need to be either chronic or extremely severe in order to have a significant effect on postnatal development. While stronger effects on behavior will usually result from more severe and prolonged prenatal exposure to stress, significant and lasting effects have been produced by rather moderate and brief exposures to stress. For example, to stress pregnant monkeys, Schneider et al. (1999) used events that were intended to model “recurrent daily episodic stress”—at the level that many expectant human mothers might experience from stressful life events. The investigators therefore used stressors that were neither chronic nor physically traumatic, exposing pregnant monkeys instead to brief, intermittent, and unpredictable, stimuli (loud bursts of noise) that were upsetting but did not inflict any physical injury. These stressors produced substantial adverse effects on developmental outcomes, such as reduced attention span and increased fearfulness, in the rhesus offspring. Significant and lasting effects of prenatal stress have also been produced by a single course of a synthetic stress hormone on a single day of gestation (Scheepens et al., 2003).
5.2 Prenatal Stress Can Produce a Broad Range of Postnatal Effects

As is described more fully later, prenatal exposure to such environmental stressors is associated with a range of postnatal abnormalities—in offspring behavior, brain development, and physiological response to stress. Abnormalities found in prenatally stressed monkeys include, to mention just two examples, increased behavioral signs of fearfulness when placed in a moderately stressful environment (Clarke et al., 1996), and increased postnatal response of the HPA axis to stressful stimuli (Clarke et al., 1994).

Both human and animal studies have found significant relations between prenatal stress and postnatal problems in a variety of behavioral domains, such as attention, language, and learning (see reviews by Mulder et al., 2002; Weinstock, 1997). Adverse effects of prenatal stress also include spontaneous abortion, pre- and perinatal complications, congenital anomalies, and neurological and immunological abnormalities. Prenatal stress can also have a variety of effects on brain development including, for example, delayed myelination, elevated sensitivity of the amygdala to GCs, and abnormal development of the dopaminergic system (see reviews by Glover, 1997; Herrenkohl, 1986; Mulder et al., 2002).

The adverse impact of prenatal and perinatal stress on the developing central nervous system may be a pathologic extension of the normal developmental process of epigenetic programming. In the normal gestational environment, the mother transfers glucocorticoids to the developing fetus in proportion to the adversity of her environment (Meaney & Szyf, 2005). When the environment is more challenging than normal, the flow of maternal stress hormones to the fetus increases, resulting in offspring that are more vigilant and avoidant of potentially dangerous situations, and thus better prepared for survival in a more challenging environment. However, maternal exposure to more prolonged or severe stress can cause the offspring to develop a pathological, life-long hyperactivation of the HPA axis as well as elevation of stress hormone levels (Seckl & Meaney, 2006).

5.3 The Timing of Prenatal Exposure Affects the Outcome

The importance of the timing of a prenatal exposure is indicated by principles of teratogenesis based on extensive experiments with animals as well as epidemiological studies of humans. One key principle is that the same teratogen can produce serious congenital anomalies if exposure occurs during sensitive periods in gestation, but have little or no effect if exposure occurs during other periods. A classic example of this principle in humans is the effects of the drug thalidomide, which produces a wide range of severe congenital defects, depending on the precise period of gestation during which the embryo is exposed. The importance of timing is also seen in the fact that different teratogens can produce a similar congenital anomaly if exposure occurs at the same prenatal period (Oster-Granite, 1988; Shepard, 1986).

Experiments with animals indicate that different brain regions vary with respect to the periods of gestation when a region is most sensitive to the effects of stress (see review by Matthews, 2000). In rhesus monkeys, for example, exposure to the same stressor was found to have greater effects on postnatal motor development if it occurred earlier in gestation, when neuronal migration is at its peak, than if it occurred in mid- to late gestation, when synaptogenesis is at its peak (Schneider et al., 1999). Thus exposure to the same teratogen, such as maternal stress, is likely to have a different effect on different behavioral domains, such as motor or language processes, depending on when exposure occurs. It should be noted that the timing of vulnerable gestational periods in humans differs significantly from that in non-human primates, because the latter are born at a more mature level of development than are humans.

Periods of prenatal vulnerability are also influenced by the placental barrier that modulates embryonic and fetal exposure to stress hormones during early and middle gestation. At a point
near the end of mid-gestation, coinciding with the end of neurogenesis, this barrier becomes less active and the fetus is more likely to be exposed to fluctuating levels of maternal GCs. In humans this occurs between approximately weeks 19 and 26 (Seckl & Meaney, 2006). This transitional period presents a window of vulnerability during which extreme levels of maternal GCs could be more likely to interfere with normal neurodevelopment. It is worth noting that Kinney et al. (2008) found that environmental stress during a similar gestational period significantly increased the risk of AD.

5.4 Prenatal Stress is Also Associated with Psychiatric Disorders Other Than AD

A number of studies have found that the offspring of women who were exposed to particularly stressful life events during pregnancy are significantly more likely to develop psychiatric disorders. Huttunen & Niskanen (1978), for example, found that 167 Finnish index individuals who were in utero when their fathers died were significantly more likely to be treated for a psychiatric condition (24 cases) than were 168 control individuals who were infants when their fathers died (only 11 cases) (p < .025). Moreover, most of the 24 index cases who were treated for mental disorders, including all of those who were hospitalized with a diagnosis of schizophrenia, were, at the time their fathers died, in one of two prenatal periods: either in a period of several weeks near the middle of gestation or in the several weeks near the end. The investigators suggested that these periods could represent particularly vulnerable stages of prenatal brain development during which exposure to prenatal stressors is more likely to increase the risk of developing psychiatric disorders such as schizophrenia after birth.

Kinney (2001) investigated whether prenatal exposure to a stressful life event increases risk for schizophrenia, using as a natural experiment a particularly destructive tornado that struck heavily populated areas of the Worcester, Massachusetts area in 1953, causing more than 1000 casualties and leaving more than 10,000 people homeless. The prevalence of schizophrenia was significantly elevated in the index cohort that was exposed in utero to the tornado, compared with control cohorts with no prenatal storm exposure who were born in the same areas as the index cohorts, but in years just before and after the index cohort. The prevalence of schizophrenia was particularly high for the cohorts that were exposed to the tornado during the gestational periods identified by Huttunen & Niskanen (1978) as being more vulnerable to effects of prenatal stress. Van Os and Selten (1998) also found a significant increase in schizophrenia prevalence in a Dutch index cohort that had prenatal exposure to a presumably stressful life event, the German military invasion of the country in WW II in May 1940, compared to control cohorts born in years just before and after the index cohort.

Watson et al. (1999) found that subjects exposed to a major earthquake while in utero had significantly increased levels of severe depression and overall depressive symptoms compared to non-exposed controls. The investigators compared 611 high school seniors who had been prenatally exposed to a severe, magnitude 7.8 earthquake in Tangshan, China in 1976, to 604 matched control students who were born exactly one year after the students in the exposed group. The rate of severe depression was significantly higher in the exposed group (13.3%) than in the control group (5.5%) (p < 0.001).

A significant association between prenatal stress and increased risk for attention deficit/hyperactivity disorder (ADHD) was found in two prospective longitudinal studies. Van den Bergh and Marcoen (2004) gave the State Trait Anxiety Inventory to mothers during pregnancy as well as after the child’s birth. ADHD symptoms in each child at age 8 or 9 were rated by the child’s mother, teacher, and an external observer. Maternal anxiety during pregnancy accounted for 22% of the variance in ADHD symptoms, even after controlling for the child’s gender, parents’ education levels, smoking during pregnancy, birth weight, and postnatal maternal anxiety. Similar results were obtained by Rodríguez and Bohlin (2005), who prospectively assessed maternal stress at six points during pregnancy using the Swedish 10-
point version of the Perceived Stress Scale. Subsequently, each child was rated at age 7 by his or her mother and school teacher on 18 symptoms related to criteria for ADHD in DSM-IV-TR. Higher levels of both individual ADHD symptoms and a diagnosis of ADHD were associated with more prenatal exposure to stress ($p < .01$), with a stronger effect found for males.

### 5.5 Prenatal Stress Can Cause Behaviors Similar to Key Symptoms of AD

Many studies have found that prenatal stress can produce postnatal behaviors that resemble key features of AD (reviewed by Mulder et al., 2002; Weinstock, 2002). As noted earlier, one defining diagnostic feature of AD is impairment in reciprocal social interactions. Prenatal stress has repeatedly been found to increase the rates of abnormal social interaction in experiments with laboratory animals. For example, Clarke et al. (1996) found that when juvenile monkeys were exposed to a novel playroom environment, those that had been prenatally stressed showed significantly less appropriate social interaction than did controls who had experienced no prenatal stress. Similar effects have been found in rodents (Weinstock, 1997; 2002; Takahashi et al., 1992), for example, found that prenatally stressed rats took longer to initiate social play than did control rats.

Several studies with children have reported an association between prenatal stress and increased risk of emotional and behavioral problems. For example, O’Connor et al. (2003) examined the association between maternal anxiety and emotional and behavior problems in over 6000 English children in a large-scale prospective longitudinal study that has followed a cohort of children from gestation through childhood. Mothers completed a self-rated anxiety inventory (the Crown-Crisp index) on several occasions during pregnancy as well as after a child was born. A significant association was found between higher levels of maternal anxiety during pregnancy and the mothers’ reports on the Strengths and Difficulties Questionnaire of more behavioral and emotional problems in their children (odds ratio = 2.16 for boys, 1.91 for girls). This association held even after controlling for postnatal maternal anxiety, obstetric complications, and family psychosocial disadvantage. Similar effects were found when the children were 4 and 7 years old, suggesting that the effects of prenatal stress were quite persistent.

Animal experiments have shown that prenatal exposure to dexamethasone (DEX), a synthetic glucocorticoid, can produce effects similar to those of prenatal exposure to natural maternal stress hormones (Matthews, 2000; Weinstock, 1997). Human studies have tracked the long-term effects of prenatal DEX exposure, which had been clinically administered to expectant mothers to manage the risk of birth complications. Compared with control children with no DEX exposure, preschool children with prenatal exposure to DEX were reported by mothers to have significantly more internalizing problems on the Child Behavior Checklist, and more shyness and emotionality on the EAS Temperament Survey for Children (Trautman et al., 1995).

Two complementary lines of evidence suggest that (a) AD may involve dysfunction of a brain system involved in social cognition, in which the amygdala and the orbitofrontal cortex (OFC) play key roles, and that (b) the OFC may be especially sensitive to the effects of prenatal stress, particularly in the middle of gestation. Bachevalier and Loveland (2006) proposed a neurological model of AD involving developmental dysfunction of a brain system that includes the OFC and amygdala. This system supports social cognition and monitors both one’s own emotional states and those of other people. Several lines of evidence, including the effects of lesions in animals and humans, indicate that normal operation of this OFC-amygadala axis is critical for social cognition: the amygdala is activated according to the significance of objects or events, and the OFC uses this information to guide and adjust social behavior appropriately. Behavioral deficits will vary, depending on the location, the severity, and the timing of the

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damage to this neural network, thereby potentially accounting for the heterogeneous features found in autism spectrum conditions. Damage to the OFC region, those authors suggest, can produce a fundamental deficit in AD that underlies inappropriate responses to the mental states of other people, and that impairs self-regulation of social-emotional behavior.

Further complementary evidence, presented by Mennes et al. (2006), indicates that the OFC may be a brain region particularly sensitive to the effects of prenatal stress. Mennes et al. analyzed data from a battery of cognitive tests that were administered to 49 adolescents as part of a prospective longitudinal study on the effects of prenatal stress. The children’s prenatal exposure to maternal anxiety had been assessed by administering the Dutch version of the State Trait Anxiety Inventory to the children’s mothers at three different periods of pregnancy. Prenatal exposure to a high level of maternal anxiety was significantly associated with more deficits on cognitive tasks involving either endogenous response inhibition or dual objects of attention (such as self and other). By contrast, prenatal exposure to maternal anxiety was not significantly correlated with performance on tests involving other cognitive functions, such as working memory. Mennes et al. (2006) also found that data from fMRI studies of regional brain activation in normal subjects performing these same cognitive tests indicated that the dorsal OFC was only activated by those tests for which deficits were associated with prenatal exposure to maternal anxiety. Thus these data suggested that prenatal stress may be particularly likely to disrupt development of the OFC, which in turn plays a key role in social cognition processes that are dysfunctional in AD.

Qualitative deficits in the development of communication, particularly spoken language, are a second essential symptom of AD. A prospective longitudinal study by King and her colleagues at McGill University (Laplante et al., 2004) has been following a group of 55 children who were in utero when their mothers were exposed to a severe ice storm that hit southern Quebec in January 1998. The investigators divided the children into low vs. high exposure groups, based on maternal reports of objective storm-related stressors such as property damage, days without electricity, and family separation. Prenatal exposure to a high level of objective, storm-caused stress was associated with significantly poorer language test performance at age 2 years on the MacArthur Communication Development Inventory, accounting for 12% of the variance in productive language ability (p < 0.01) and 17% of receptive language ability (number of words comprehended) (p < 0.01).

While it is obviously difficult to study effects of prenatal stress on the development of language in non-humans, effects on brain lateralization can be studied and are of interest because language acquisition in humans depends on developmental processes that involve a significant degree of hemispheric lateralization and specialization of function. Fride and Weinstock (1988) found that prenatal stress in rats produced marked changes in cerebral lateralization, with changes in left-right differences in dopaminergic activity in three brain regions, including the prefrontal cortex. Glover et al. (2004) found that maternal reports of anxiety at 18 weeks of gestation predicted an increased likelihood of an indicator of atypical lateralization--mixed-handedness--in children assessed at 42 months after birth. This prediction held true even after controlling for parental handedness and postnatal maternal anxiety (odds ratio = 1.23, p < 0.05). These results complement findings of more mixed handedness in AD (Soper et al., 1986).

A third defining characteristic of AD is an increase of repetitive or stereotyped behaviors, a preference for sameness and routine, and a tendency to experience marked distress over minor or trivial changes in the environment. In their study of children exposed in utero to the Quebec ice storm, King and Laplante (2005) videotaped a non-structured free-play task when the children were two years old. Children who had high prenatal storm exposure showed significantly more stereotypic play (banging, waving, or mouthing objects), and significantly
less functional play (using objects according to their intended function; e.g., pouring imaginary tea from a toy pot into a cup), than children with lower storm exposure. For children exposed in the 2nd trimester, the level of objective maternal stress accounted for 54% of the variance in the level of children’s functional toy play.

Several experiments with laboratory animals found similar effects; e.g., when Clarke et al. (1996) introduced infant monkeys that had been prenatally stressed into a novel playroom, these monkeys were much less likely than control monkeys to explore the playroom and play with the novel toys ($p < .001$). Unlike the prenatally stressed monkeys, who remained inhibited and showed virtually no increase in exploration over a period of 30 minutes, control monkeys quickly became less fearful in the playroom, and after several minutes in the room they were spending four to five times more minutes in exploration than the prenatally stressed group of monkeys. Schneider et al. (2004) found that when juvenile monkeys were stressed by being separated from their mothers for weaning, baseline plasma levels of adrenocorticotropic hormone (ACTH) were highly correlated with rates of stereotyped behaviors. This study also found that prenatally stressed monkeys displayed less exploratory activity and more stereotypic behavior in a stressful environment. In a review of stereotyped, or “compulsive,” behaviors in animals, Luescher (2000) concluded that exposure to psychologically stressful environments and the presence of an anxious temperament in an individual both contribute to increased rates of compulsive behaviors.

In summary, many different studies—involving different species, research designs, types of prenatal stressors, and measures of postnatal sensitivity to stress—have found that prenatal stress tends to make individuals hyper-aroused when faced with novel or challenging postnatal stimuli. Individuals that are hyper-aroused are, in turn, more likely to engage in stereotyped motor behaviors.

6. Postnatal Hypersensitivity to Stress: A Marked Effect of Prenatal Stress

While prenatal stress can produce a wide range of behavioral, endocrinological, and anatomical outcomes, it tends to have particularly strong effects on the systems that mediate the organism’s response to stress.

6.1 Animal Studies

As described earlier, both children and infant monkeys that have been prenatally stressed tend to display greater anxiety when placed in unfamiliar situations. A analogous pattern is found in rodents. Weinstock (2002) noted that, in rats, prenatal stress significantly increased postnatal fear of strange situtions, as manifested on several different behavioral measures, including decreased exploration in an open field and more defensive withdrawal from threatening environments. Son et al. (2007) similarly found that adult male mice with prenatal exposure to stress had impaired motor response habituation to a novel stimulus ($p < 0.05$).

Prenatally stressed individuals also have a stronger and more prolonged release of stress-related hormones in response to stressful situations. As Mulder et al. (2002) noted, prenatal stress appears to impair the ability of neuroendocrine systems to regulate responses to stressful stimuli postnatally, resulting in exaggerated hormonal and behavioral responses to such stressful stimuli. Weinstock (1997), in reviewing research on laboratory animals, concluded that prenatal stress is associated with postnatal hyperanxiety, and that the effects of prenatal stress can also be produced by directly exposing pregnant animals to hormones, such as GCs, that are released in reaction to these psychologically stressful situations.
6.2 Hypersensitivity to Stress: An Important Vulnerability to AD?

The effect of prenatal stress on postnatal HPA-axis reactivity and sensitivity to stress is especially interesting, for two reasons. First, several studies have reported that hypersensitivity to stress is associated with AD. For example, Corbett et al. (2006) found that AD children were more likely than control children to show HPA-axis hyperactivity in response to novel stimuli. This study examined changes in salivary cortisol and found that AD children showed elevations in cortisol following exposure to a novel non-social situation, whereas control children did not \((p < 0.05)\). Richdale & Prior (1992) found a tendency in children with high-functioning autism toward cortisol hypersecretion during the daytime hours. This effect was principally found in those children who were integrated into the normal school system, which the authors suggested indicates that the elevated cortisol secretion was a response to environmental stress.

Second, based on clinical work with AD children, Zelazo (2001) has hypothesized that hypersensitivity in infants may be a crucial predisposing factor that causally contributes to the development of AD. Zelazo has proposed a developmental model of AD in which low stress tolerance in a young child leads to abnormal patterns of social avoidance and behavioral noncompliance, patterns which in turn disrupt child-caretaker interactions that are necessary for acquisition of social and language skills.

This developmental model of AD was supported by the results of a prospective study of 41 children with pervasive developmental disorders of unknown etiology and autistic symptoms (Zelazo, 1997). When they were enrolled in the study at age 22 or 32 months, the children had delays of at least 4 months on the Bayley Scales of Infant Development. However, 31 of these children performed at age-appropriate levels on a test of visual information processing that did not require language, which suggested that their delays on the Bayley, a standard test of mental development, did not reflect a general deficit in cognitive ability. This interpretation was supported by the fact that most of these 31 children subsequently showed marked gains in their IQ test scores after they and their parents were enrolled in an intervention program in which the parents were taught to spend 12 minutes per day for several days a week, systematically using praise and other forms of positive reinforcement to encourage their children’s stress tolerance, cooperation, and expressive language. At follow-up testing 18-months later, 61% of these 31 children with intact information processing capacity now scored \textit{at or above} their chronological age level on conventional (Bayley or Stanford Binet) intelligence tests (Zelazo, 1997).

In summary, the postnatal effects of prenatal stress tend to include not only an increase in the behavioral signs of anxiety—both at baseline and in response to psychologically stressful situations—but also in chronically increased levels of stress hormones and higher rates of anatomical abnormalities in brain regions that play an important role in modulating behavioral responses to stress. If prenatal stress contributes to AD, one would expect to see signs of such hypersensitivity to stress in children with AD, and in fact such signs have been reported by several studies using different methods and research designs.

7. Prenatal Stress Can Produce Other Abnormalities Commonly Found in AD

In addition to contributing to behaviors that resemble essential symptoms of AD, prenatal stress is also associated with an increased risk of developing other conditions that tend to be associated with AD, such as abnormalities in cognitive, neurological, and immune functions.

7.1 Cognitive Abnormalities

Cognitive and attentional deficits are found in most people with AD, and as many as 70% of children with AD also have co-occurring mental retardation, as assessed by conventional IQ tests (APA, 2000; Chakrabarti & Fombonne, 2001). Observational studies with humans, as...
well as experiments with animals, have found that prenatal stress is associated with cognitive
deficits. In lab experiments with monkeys, both prenatal exposure to environmental stressors
and the injection of ACTH in the middle of gestation produced cognitive deficits, impaired
attention, and increased distractibility in offspring. For example, Schneider et al. (1999) found
that infant rhesus monkeys that had been prenatally stressed scored significantly worse than
controls on a battery of test measures of neuromotor maturity and attention (e.g., ability to
orient to and follow moving objects) that were designed to parallel items on a widely used
behavioral assessment scale designed for human infants. Prenatally stressed rats have also
shown delayed learning in a task requiring spatial memory (Lemaire et al., 2000).

A prospective longitudinal study of children by Buitelaar et al. (2003) found significant
associations between prenatal stress and infants’ cognitive development. Mothers completed
questionnaires at three points during pregnancy, and then again at three points after giving
birth, on the frequency of their daily hassles, pregnancy-specific anxiety, and perceived level
of stress. Exposure to environmental stress in early or mid-gestation was associated with an
average decrease of eight points on the Mental Development Index (MDI) of the Bayley Scales
at age 8 months. In addition, higher levels of maternal salivary cortisol during late pregnancy
predicted lower mental development scores in the infants as well as poorer levels (14.6% of
the variance) of maternally-reported adaptability in the infants. In the Quebec ice storm study
noted earlier, Laplante et al. (2004) found that children who were exposed prenatally to
moderate to high levels of objective storm-related stress had a significantly lower mean Bayley
MDI score at age 2 than children of mothers reporting low stress (19.5 points lower if the stress
occurred in the 2nd trimester). The level of prenatal stress in the 2nd trimester accounted for
41% of the variance in Bayley MDI scores.

7.2 Seizure Disorders and Other Neurological Abnormalities

Minshew et al. (2005) pointed out that epilepsy is found in about a third of people with AD,
compared with a prevalence of only 2% to 3% in the general population. Several experimental
studies with laboratory animals have reported that prenatal stress produces a significantly
greater risk of developing seizures after birth. For example, Edwards et al. (2002) found that
prenatal stress in rats significantly lowered seizure thresholds and increased the development
of kindled seizures in both infant and adult rats. By contrast, exposure to postnatal stress had
no significant effect on either seizure thresholds or kindling rate. Frye and Bayon (1999)
exposed rats to 20 minutes of restraint stress towards the end of their pregnancy. They found
that the prenatally stressed offspring had more partial seizures and more tonic clonic seizures
of long duration than did control rats.

In reviewing MRI studies of brain anatomy of patients with AD, Brambilla et al. (2003)
concluded that the most consistently replicated findings included structural abnormalities of
the cerebellum and corpus callosum. Similarly, Eigsti and Shapiro (2003) concluded that a
cerebellar abnormality was the most consistent neuropathologic finding in histological studies
of postmortem brain tissue in AD. It is therefore notable that experiments with lab animals
have found that prenatal stress can produce abnormalities in both the cerebellum (Ahlbom et
al., 2000) and the corpus callosum (Coe et al., 2002). Prenatal exposure to GCs also has adverse
effects on cerebellar development and function (e.g., Ahlbom et al., 2000). Research in rhesus
monkeys has found that prenatal exposure to DEX caused degeneration of neurons in the
hippocampus (Uno et al., 1994), another brain region that Brambilla et al. (2003) noted as being
reported to be significantly reduced in size in individuals with AD.

7.3 Immunologic and Neuroinflammatory Abnormalities

Analyses of post-mortem brain tissue of AD patients (Vargas et al., 2005) have found signs of
neuroinflammatory activity in the cerebellum and cerebral cortex. Microglia were consistently
activated in all brain regions—particularly in the cerebellum, where a loss of neurons in the Purkinje cell layer and granule cell layer was apparent in 9 of the 10 AD brains. In addition, the cerebrospinal fluid of AD patients was found to have a unique proinflammatory profile of cytokines. Experiments with lab animals have reported that prenatal stress can produce lasting abnormalities in immune function, including neuroinflammation, in offspring. For example, Kay et al. (1998) found that adult rats that had been prenatally stressed showed decreased natural killer cell activity in splenic and blood lymphocytes, and decreased proliferation of splenic lymphocytes, compared to control rats.

In rhesus monkeys, prenatal exposure to either stress hormones or psychological stress of the mother by exposure to loud and unpredictable noises, produced significant abnormalities in postnatal immune function in both infancy and late childhood (Coe & Lubach, 2005). Prenatal stressors caused disturbances in many immune responses, including proliferation of lymphocytes, natural killer cell activity, and production of cytokines, impairing the monkeys’ ability to fight off viral and bacterial infections. Prenatal stress also reduced the establishment of beneficial intestinal microflora and increased the risk of enteric infections (a finding of possible interest in light of reports of increased gastrointestinal problems in AD).

As noted earlier, prenatal stress leads to increased postnatal HPA-axis activation and stress response, and these in turn are associated with neuroinflammation. Stress can affect microglia, which are important for regulation of CNS neuroinflammation. Activated microglia may contribute to the neuronal damage in neurodegenerative diseases, via excess release of proinflammatory or cytotoxic factors (Gonzalez-Scarano & Baltuch, 1999). Ock et al. (2006) noted that the stress neuropeptide corticotropin-releasing hormone (CRH) has proinflammatory effects. Those authors reported that, in vitro, CRH influences apoptosis of microglia taken from mice, suggesting that CRH may regulate neuroinflammation via this induction of apoptosis in microglia. The authors also noted that apoptosis is a regulatory mechanism that controls and limits the extent of immune and inflammatory responses. When this mechanism is dysfunctional, the immune system may attack the host, leading to tissue damage. The authors suggested that this may be a mechanism by which an elevated stress response contributes to neuroinflammatory damage.

In summary, evidence from both human and animal studies has found that prenatal stress is associated with a number of postnatal abnormalities. If prenatal stress does contribute to AD, this could help explain why many abnormalities that prenatal stress can cause—such as cognitive deficits, seizure disorders, and neuroinflammatory problems—have such high rates in AD.

8. Mechanisms by Which Prenatal Stress Can Disrupt Fetal Brain Development

Experiments with laboratory animals indicate that prenatal stress can disrupt brain development through several mechanisms (Mulder et al., 2002). The neuroinflammatory effects just noted represent one mechanism. Prenatal stress can also (a) reduce uterine and placental circulation, inducing fetal hypoxia; (b) stimulate the release of maternal stress hormones that can cross the placenta and alter the development of the HPA axis; (c) produce complications of pregnancy and delivery; and (d) have epigenetic effects on the expression of genes involved in stress response. Stress can also (e) disrupt the normal patterns of prenatal exposure to sex hormones that program typical sex differences in brain structure and function, which tend to be atypical in children with AD.
8.1 Reduced Blood Flow to the Uterus and Placenta
Several studies (e.g., Glasson et al., 2004; Juul-Dam et al., 2001) have found increased rates of perinatal hypoxia among AD children. Maternal stress and the resultant release of catecholamines can cause uterine vasoconstriction and reduced blood flow to the placenta, resulting in fetal hypoxia and a spectrum of fetal injuries that range from spontaneous abortion to varying degrees of cerebral damage (Mulder et al., 2002; Uno et al., 1994).

8.2 Programming of the Fetal HPA Axis
Maternal stress stimulates release of GCs that can pass across the placenta and affect the developing fetus if GC levels are high enough to overcome the action of fetal enzymes that protect against GCs. The HPA axis is particularly sensitive to effects of prenatal exposure to excess levels of GCs (Matthews, 2000). Prenatal exposure to environmental stress or GCs can lead to postnatal HPA hyperactivity in response to stress (Langley-Evans, 1997).

8.3 Obstetric Complications
Environmental stress can produce complications of labor and delivery that are associated with greater risk of hypoxia and cerebral hemorrhage in the newborn, and experiments with both animals and humans show that pre- or perinatal stress can cause OCs. For example, birth weight can be lowered in laboratory animals by either exposing a pregnant mother to environmental stressors or by injecting her with GCs (e.g., Aghajafari et al., 2002). Experiments with mammals have shown that stressful environmental disturbances during parturition can also significantly disrupt and delay labor (e.g., Lawrence et al., 1992; Newton et al., 1968). A number of prospective studies in humans have found that maternal stress is associated with increased rates of OCs (see reviews by Lobel et al., 2000; Talge et al., 2007). Conversely, a controlled clinical trial conducted by Kennell et al. (1991) showed that provision of emotional support to women during labor and delivery can significantly reduce the incidence of perinatal OCs. Experiments with animals have shown that OCs such as Cesarean sections in turn can produce abnormalities in postnatal behavior that resemble those seen in AD, such as increased social withdrawal and behavioral stereotypy (Laviola et al., 2004). Brake et al. (1997) found that in rats perinatal complications associated with perinatal anoxia increased the sensitivity of mesolimbic dopamine neurons to stress in adults. Thus labor and delivery complications, as well as prenatal exposure to environmental stress, can increase a developing mammal's sensitivity to stress after birth.

8.4 Epigenetic Effects on the Stress Response
In laboratory animals, prenatal exposure to high levels of GCs has been found to have long-term, even lifelong, effects on modulation of the HPA axis. One mechanism for this effect is alteration of gene expression in neurons (Meaney & Szyf, 2005). Glucocorticoid receptors (GRs) in the hippocampus act as a mediator of CRH production. In rats, perinatal exposure to stress can produce lasting changes in GR gene expression in the hippocampus, altering the threshold for activation of the HPA (see review by Welberg & Seckl, 2001).

8.5 Prenatal Stress Can Affect Fetal Exposure to Testosterone
There is some evidence that individuals with AD tend to have extreme variations of psychological and neuroanatomical characteristics that are more common in males than females, and that risk for AD may be increased by fetal exposure to high levels of testosterone during critical periods of gestation (Baron-Cohen et al., 2005; Knickmeyer & Baron-Cohen, 2006). This evidence supports the “extreme male brain” theory of AD (Baron-Cohen, 2002), which proposes that elevated fetal testosterone levels are positively correlated with symptoms of AD and negatively correlated with social development and empathy (Ingudomnukul et al., 2007). It is therefore notable that there are convergent lines of evidence, from studies using...
complementary research designs, showing that stress in pregnant women is likely to increase fetal levels of testosterone. For example, in a clinical trial with random assignment, women who received a 10-week stress management intervention showed a significant reduction in serum testosterone level, whereas women on a wait-list control group showed no change (Cruess et al., 2000). In amniotic fluid collected from pregnant women undergoing amniocentesis, cortisol and testosterone levels were significantly and positively correlated (Sarkar et al., 2007).

Thus there are several well-established physiological mechanisms by which prenatal stress can influence early development. This evidence comes from a variety of studies, including experiments with laboratory animals, prospective longitudinal studies with children, and in some cases even randomized clinical trials with pregnant women and their children.

9. Can Prenatal Stress Help Explain Other Risk Factors for AD?

Converging lines of evidence suggest that prenatal stress might be a common factor that helps to mediate the association of AD with several of its previously identified risk factors.

9.1 Obstetric Complications (OCs) and the Risk for AD

More than a dozen careful studies have investigated rates of pre- and perinatal OCs in AD; most of these studies have found that OCs were significantly more prevalent in AD children than in various control groups, including the AD probands’ own siblings (e.g., Glasson et al., 2004; Hultman et al., 2002; Juul-Daam et al., 2001; Larsson et al., 2005; Nelson, 1991; Torrey et al., 1975). Both prenatal and perinatal OCs have been found to be elevated in AD. As noted earlier, evidence that elevated levels of prenatal stress can lead to OCs has been found in animal experiments, prospective human studies, and clinical trials. Thus the same exposure to prenatal stress that increases risk for AD may also increase risk of OCs.

9.2 Gender Differences in Risk for AD

Males are at a significantly higher risk for AD than females, by a factor of about 4:1 (Fombonne, 2005). There are theoretical and empirical grounds for thinking that pre- and perinatal stressors might result in AD more frequently in males. First, there is evidence that the male fetus and infant are biologically more vulnerable to prenatal stress than their female counterparts. For example, Clarke et al. (1996) found that the adverse effects of prenatal stress on the behavior of juvenile rhesus monkeys – when exposed to the novel playroom environment noted earlier – were more severe for males than females. Experiments with rodents also found that males tend to be more vulnerable to the effects of prenatal stress (Weinstock et al., 1988).

Complementary results have been reported in children. For example, Van den Bergh & Marcoen (2004) found that prenatal exposure to stress was associated with development of significantly more ADHD symptoms, with a much stronger effect found in boys than girls. In the study noted earlier by Watson et al. (1999), which found significantly higher rates of depression in high school students following prenatal exposure to a severe earthquake, the rate of depression was significantly increased only in males. There are also sex differences in the effects of prenatal stress on brain development and morphology. For example, prenatal exposure to a synthetic corticosteroid depressed brain growth significantly more in male than in female rats (Scheepens et al., 2003). Sex differences in the programming of the HPA axis by prenatal stress have also been found (Seckl & Meaney, 2006). In monkeys, prenatal stress produced different effects on the volume of the corpus callosum depending on the sex of the offspring—a significant decrease for males, but an increase for females (Coe et al., 2002). A smaller mean volume of the corpus collosum has been reported in individuals with AD (Vidal et al., 2006).
If prenatal environmental factors play a relatively more important etiologic role in males than females with AD, then genetic factors would conversely be expected to be relatively more important in females with the disorder, so that females with AD should be more likely to have a family history of AD. Consistent with this, Ritvo et al. (1989) found that the rate of AD in the siblings of female probands with AD was twice as high as in the siblings of male probands.

9.3 Maternal Fertility Problems and Risk for AD

Several studies have reported that maternal fertility problems are a risk factor for AD. Croughan et al. (2006) studied 2,000 mothers who had a history of infertility and found that these women were significantly more likely than demographically matched controls to have had a child who developed a severe disorder, including AD. It is therefore of interest that stress itself can lead to fertility problems. Multiple experiments with lab animals, reviewed by deCatanzaro and MacNiven (1992), found that exposing pregnant animals to environmental stress or ACTH resulted in increased embryo resorption and smaller litter size. Similarly, Nepomnaschy et al. (2006) found that, in women, increased urinary cortisol during the first three weeks after conception was associated with a significantly higher rate of spontaneous abortion.

Moreover, several studies have demonstrated that infertility is itself stressful. For example, Domar et al. (1992) found that depression rates in infertile women were twice as high as in control women. Domar et al. (1993) found that anxiety and depression levels in infertile women were comparable to the levels present in women with cancer or coronary heart disease. Freeman et al. (1985) found that about half of women undergoing fertility treatment rated their infertility as the most stressful experience of their lives. Campagne (2006) concluded that the evidence linking stress to fertility problems was strong enough that efforts to reduce stress should be the first approach to treating infertile couples, prior to attempting more invasive procedures such as *in vitro* fertilization. Thus several lines of evidence indicate that women who have had difficulty having children will tend to have elevated levels of anxiety about potential difficulties with their current pregnancy. If infertility has been the result of recurrent maternal stress, the same stress may be a risk factor for AD in the child of a subsequent pregnancy that is carried to term.

In summary, if prenatal stress does contribute to AD, this could help to explain why (a) OCs tend to increase the risk for AD, (b) AD is 3–4 times more common in males than females, and (c) parental fertility problems are associated with increased risk of having a child with AD.

10. Factors That May Moderate the Effect of Prenatal Stress on Risk for AD

Several factors are likely to moderate how prenatal exposure to stressful events affects prenatal development and the risk for AD. One such moderating factor is likely to be the genetic susceptibility of mother and fetus. In animals, there are well established genetic strain differences that influence the behavioral and endocrine responses of individuals to stress.

Recent research has found evidence for interactions between genes and the postnatal environment in the etiology and pathogenesis of other mental disorders, such as major depression. For example, Rutter et al. (2006) reviewed several studies that found evidence for an interaction of this kind. These studies found that individuals who carry a short allele of the serotonin transporter (SERT) gene are much more likely than non-carriers of this allele to become depressed if they have been exposed to stressful life events. In most studies, this SERT allele was not associated with an overall increase in depression, but rather was only associated with an increase in combination with exposure to adverse life events. Several studies have reported that the “short” SERT alleles are more common in children with AD than in control samples, though other studies have not been able to replicate these results (see review by
Freitag, 2007). While there are, to our knowledge, no reports of such interactions between genes and the prenatal environment in AD, they deserve serious attention in future research.

Teasing apart the roles of genetic factors from those of the pre- and postnatal environments can be difficult, as these factors tend to be confounded in most samples. Adoption studies can often be helpful in this respect. In the case of ADHD, for example, Sprich et al. (2002) conducted an adoption study with results that indicated that the strong tendency for ADHD to run in families was due to shared genes or prenatal environments, rather than shared postnatal environments, as the prevalence of ADHD was several times higher in the ADHD children’s biological parents than in their adoptive parents. Jacobsen and Kinney (1980) found that adoptees who developed schizophrenia were significantly more likely than control adoptees to have experienced pre- or postnatal exposure to maternal obstetrical complications. This was the case even though the adoptees had been separated from their biological parents shortly after birth and the adoptees had been matched for the socioeconomic status of the adoptive parents. These results suggest that the elevated rates of pre- and perinatal complications in schizophrenia patients that have been reported in many studies were not due simply to a tendency for children who experience more difficult prenatal environments to also experience more postnatal adversity. Adoption studies may be less helpful, however, in separating the effects of the prenatal environmental from those of genetic factors. For this purpose, the use of natural experiments, such as the disasters noted earlier, may be especially helpful.

How a pregnant woman’s exposure to a stressful life event affects the embryo or fetus she is carrying is also likely to depend to a significant degree on how she herself responds to that event. The same life event will tend to produce greater stress on the mother—and hence potentially on the embryo or fetus—if she has fewer personal and social resources to help cope with the stressful events. Nuckolls et al. (1972) assessed the psychosocial assets of 170 women early in their pregnancies, and then tracked stressful life changes during the course of their pregnancies. Psychosocial assets included levels of support from spouse, parent, siblings, in-laws, and friends, as well as the woman’s confidence in her financial and emotional supports and in her physician. Among women with high life change scores during pregnancy, only 33% of those with strong social assets experienced birth complications, whereas 91% of those with weak social assets had complications. These results could not be explained by differences in the women’s age or social class.

Another factor likely to strongly influence the effect of prenatal stress is the timing of exposure to the stressful event. As noted earlier, previous research has found in many cases that the risks for psychiatric disorders associated with prenatal exposure to stressful events were greatest if exposure occurred during certain periods of gestation.

**11. Implications for Prevention and Treatment**

If pre- and perinatal exposure to stressful events is shown to be a significant risk factor for AD, this could have a number of important clinical implications for prevention and treatment.

**11.1 Implications for Prevention**

Several considerations suggest that efforts to prevent AD by ameliorating prenatal stress could be worth investigating. Compared with efforts to reduce genetic risk factors for AD, efforts focused on prenatal and perinatal care factors may offer both ethical and economic advantages. Even for medical disorders with a well-established genetic basis (e.g., trisomy 21 and Tay-Sachs disease), prevention efforts that focus strictly on countering genetic risks can be costly, may involve additional risks to the mother and fetus (as in amniocentesis), or pose choices, such as therapeutic abortion, that can be emotionally and ethically problematic for many people. By contrast, helping expectant mothers to avoid or cope with stressful events could be...
a less problematic, less risky, and less costly approach to prevention, particularly if it could focus on relatively narrow time frames during gestation that research indicates are periods of special vulnerability to stress. Such interventions could be further focused on pregnancies that were at high risk for AD for other reasons, such as genetic liability or family history.

It may be possible to ameliorate certain sources of environmental stress by providing social or financial support to help a pregnant woman cope with life events. If one could effectively identify pregnancies at high risk for AD and substantially reduce the risk of AD in the offspring of those pregnancies, the economic benefit could be very great, because the lifetime costs of AD are so high that the benefits of preventing even a single case of AD are enormous.

11.2 Implications for Wise Use of Genetic Risk Factors in AD

Once genes that increase liability for AD actually have been identified, a key question will be how that information can best be used for prevention. Geneticists such as Francis Collins, Director of the Human Genome Project, and Nobel laureate James Watson, have pointed out the potential dangers of “negative” eugenic approaches that emphasize removal from the gene pool of alleles that increase liability for non-Mendelian psychiatric disorders (e.g., see Jamison, 1998). Pauls (2002) has suggested that a more fruitful approach to applying knowledge about liability genes may lie in another direction, namely, in identifying crucial interactions between environmental factors and these genes, in order to tailor interventions that provide optimal environments for individuals who carry these genes. But do some of the most crucial gene-environment interactions occur during the pre- and perinatal periods of development? Efforts to answer this question should be a high priority of research on AD, given that key genetic and environmental factors in this disorder appear to exert their effects on the developing brain near, or even before, birth.

11.3 Implications for Treatment and Early Intervention

Abnormally low stress tolerance in a developing child may also play a key role in AD by inhibiting the normal postnatal development of expressive language and self-regulation. As noted earlier, Zelazo (2001) has proposed a developmental model of AD in which the core congenital problem in most children who develop AD involves an unusually low stress tolerance, which leads to abnormal patterns of avoidance, withdrawal, and behavioral noncompliance such as temper tantrums. These patterns of behavior, in turn, interfere with the child’s normative interactions with his or her caretakers and caretaking environment that are crucial for the development of expressive language skills. The disruptive behaviors result in stronger reinforcement of avoidance, and further prevent the child from experiencing and learning to tolerate stress. Thus, abnormally low levels of stress tolerance, which is also observed in these children’s high sensitivity to various novel stimuli, may interfere with children’s interactions with the environment in a negatively cascading way that results in deficits associated with AD, such as impairments in development of expressive language ability as well as impaired ability for self-regulation.

The research reviewed in this review paper is largely consistent with the hypothesis that children with AD tend to have postnatal hypersensitivity to stress. This in turn supports the view proposed by Zelazo et al (2001), as well as clinical observations of AD children, that early behavioral interventions to increase a child’s stress tolerance may represent a promising approach to treating children who have, or are at high risk for, AD. There is also experimental evidence from research with animals that the effects of prenatal stress on hypersensitivity can be remediated by early behavioral therapeutic intervention. For example, Weinstock et al. (1988) found that while prenatally stressed rats showed significantly greater signs of fear on postnatal tests, these effects could be ameliorated by simple postnatal interventions, such as (a) gentle handling by humans for a few minutes each day for three weeks after birth, or (b)
placing the newborn pups with foster mothers, who spent more time licking the pups than did the pups’ biological mothers who had been stressed.

Because early intervention can be an important factor in improving outcome in children with AD (Bryson et al., 2003; Landa, 2007), children who were exposed to prenatal stress could be high-priority candidates for proactive early intervention programs, perhaps even before they are old enough to be definitively diagnosed with AD. This is especially true if the exposure is accompanied by other risk factors such as familial history of autistic symptoms or a high maternal level of trait anxiety, among other putative risk factors.

12. Directions for Future Research

Studies to date on prenatal stress and AD, while yielding significant evidence for an association, nonetheless had key limitations. New research is needed to address these limitations. For example, high levels of stressful events reported by mothers during their pregnancies with AD children (Ward, 1990; Beversdorf et al, 2005) could have been due to biased retrospective reports by mothers. To control for this possibility, one approach would be to ask mothers about life events that occurred during children’s infancies as well as during specific months of their gestations. Since some popular theories of causation of AD emphasized by the mass media and parent support groups tend to emphasize postnatal exposures (e.g., vaccines) rather than prenatal ones, any reporting biases are likely to lead mothers to over-report events in their children’s infancies rather than in their gestations. A complementary approach to controlling for possible maternal reporting bias would be prospective longitudinal studies of children, beginning when the children are still in utero. However, because the baseline prevalence of AD is less than 1%, this approach is likely to require very large samples sizes for good statistical power. Studies with smaller sample sizes could be used by including AD probands’ siblings, who have a higher risk of AD.

Future research also needs to investigate other factors, such as (a) a mother’s social resources for coping with stressful life events that could affect the resultant distress experienced by the mother (and harmful effects on the fetus), as well as (b) changes in maternal nutrition or physical health that might be affected by stressful events. To address this issue, future studies would do well to assess the levels of social support, from sources such as relatives and friends, that were available to help mothers cope with stressful events, since research noted earlier has found that such support seems to protect against the harmful effects of prenatal exposure to stressful life events. Another area not directly examined by previous research is whether prenatal stress is associated with other AD risk factors, such as OCs or family history of AD, and whether stress interacts with the presence of particular genetic variants that are associated with increased risk for AD. These would be important factors to examine in future research because, as was noted earlier, previous research suggests that one mechanism by which prenatal stress might increase AD risk would be via increasing OCs. The identification of genetic variants that are associated with increased risk for AD also presents an important research opportunity to investigate whether the effect of prenatal stress on AD depends on the child’s genotype.

13. Conclusion

In summary, empirical evidence from a wide variety of studies strongly suggests that prenatal stress may play a significant role in the etiology of AD. This evidence comes from studies involving many different investigators, research designs, and subjects, including humans and different animal species. This research indicates that prenatal stress can cause a variety of postnatal abnormalities, including not only the behaviors that resemble the defining core symptoms of AD, but also other problems, such as seizure disorders, cognitive deficits, and
abnormalities in immune function, that also have greatly elevated rates in AD. An etiological role for AD can also help to explain why certain characteristics, such as maleness, maternal OCs, and a parental history of fertility problems, are important risk factors for AD.

While the available evidence does not conclusively demonstrate that prenatal stress is a causal factor in AD, this possibility warrants serious consideration for several reasons. First, it is notable that an etiologic role for prenatal stress can help explain so many different features and risk factors associated with AD. Second, research has elucidated physiological mechanisms by which prenatal stress could produce these features of AD. Third, if prenatal stress does play a role in AD, then programs aimed at ameliorating stress in pregnancies at elevated risk for AD could be an attractive approach to primary prevention of AD. Fourth, because prenatal stress tends to produce postnatal hypersensitivity to stress, a role for prenatal stress in AD would complement other evidence indicating that postnatal hypersensitivity is an important congenital trait predisposing to AD, and that programs to increase tolerance for stress may be a valuable approach to behavioral therapy for children with AD. Therefore, further investigation of a role of prenatal stress in AD deserves high priority.

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