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Review

# Prenatal stress and risk for autism

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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.



**Contents**



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## 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 years 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 persons with AD are able to live and work independently as adults. AD is four to five times more prevalent in males than females (APA, 2000).

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 and 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 h 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 and 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 to 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 post-natal environmental pathogen causes a behavioral disorder only if an exposed individual carries a specific genetic variant (Caspi and Moffitt, 2006; Rutter et al., 2006). In one type of gene–environment interaction (Meaney and 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