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High Antenatal Maternal Anxiety Is Related to ADHD Symptoms, Externalizing Problems, and Anxiety in 8- and 9-Year-Olds

Bea R. H. Van den Bergh and Alfons Marcoen

Associations between antenatal maternal anxiety, measured with the State Trait Anxiety Inventory, and disorders in 8- and 9-year-olds were studied prospectively in 71 normal mothers and their 72 firstborns. Clinical scales were completed by the mother, the child, the teacher, and an external observer. Hierarchical multiple regression analyses showed that maternal state anxiety during pregnancy explained 22%, 15%, and 9% of the variance in cross-situational attention deficit hyperactivity disorder symptoms, externalizing problems, and self-report anxiety, respectively, even after controlling for child’s gender, parents’ educational level, smoking during pregnancy, birth weight, and postnatal maternal anxiety. Anxiety at 12 to 22 weeks postmenstrual age turned out to be a significant independent predictor whereas anxiety at 32 to 40 weeks was not. Results are consistent with a fetal programming hypothesis.

It is recognized that both genetic and nongenetic factors play an etiological role in commonly diagnosed childhood disorders, such as attention deficit hyperactivity disorder (ADHD), externalizing problems, and internalizing problems (e.g., see Bradley & Golden, 2001; Lonigan, Vasey, Phillips, & Hazen, 2004; Teichner & Golden, 2000). Because of the development of noninvasive tools to observe the fetus, techniques for observing and computing neural processes, and concomitant conceptual changes, there has been an extraordinary progress in genetics, embryology, and developmental neuroscience (Elman et al., 1998). The knowledge that during postnatal as well as during prenatal development the critical interaction of genetic constraints with internal and external environmental influences gives rise to the phenotype (Gottlieb, 1976; Gottlieb & Halpern, 2002; Johnson, 1997) has important implications (e.g., for the study of early origins of childhood disorders). It has long since been known that neurodevelopmental impairments seen in some of these disorders (e.g., impairments in attention, memory, response inhibition, processing speed) are caused by the deleterious effect of prenatal factors on developmental processes of the brain. Studies in the field of behavioral teratology have shown that the pattern of resulting behavioral and cognitive effects in the offspring is dependent on the stage of gestation at which prenatal exposure occurs, as well as on the type, dose, and duration of exposure to the teratogen (e.g., tobacco, alcohol, cocaine and other drugs, lead, methylmercury, viral and bacterial infections, nutritional deficiencies) and on differences in species and individual susceptibility (e.g., see Coyle, Wayner, & Singer, 1976; Jacobson & Jacobson, 2000; Mayes, 2002). Because of scientific progress, old questions of whether pregnant mothers’ emotional states in any way “influence the conceptus in the womb” (Montagu, 1962, p. 169) or “may contribute to the shaping of physical status, behavior patterns, and postnatal progress of the children they bear” (Sontag, 1941, p. 1002) were in the last decades reframed into the general question of whether negative maternal emotions during pregnancy should be considered as behavioral teratogens. Can high levels of maternal stress, anxiety, or depression, by triggering a cascade of physiological events in the mother, the placenta, and the fetus, deleteriously affect fetal and postnatal neurobehavioral development?
In the present study we investigated whether high maternal anxiety during pregnancy enhances the offspring’s susceptibility for childhood disorders and whether specific prenatal vulnerability periods exist. Early brain development is defined by a cascade of orderly timed processes (Levitt, 2003; Nowakowski & Hayes, 2002). Therefore, identifying periods during which the fetus is especially sensitive to the deleterious effect of high anxiety might not only have implications for preventive and therapeutic interventions in highly anxious pregnant women but also holds the potential of indirectly revealing which processes of early brain development were disturbed. This might enhance our scant knowledge (Rutter, 2001) on causal neural processes that constitute the biological underpinning of childhood disorders.

Prospective Studies Relating Antenatal Maternal Anxiety to Infant and Child Behavior, and the Fetal Programming Hypothesis in Animal and Epidemiological Research

Up to now, only the Avon Longitudinal Study of Parents and Children (ALSPAC; $N = 6,493$; O’Connor, Heron, Golding, Beveridge, & Glover, 2002; O’Connor, Heron, Golding, Glover, & the ALSPAC Study Team, 2003) has prospectively studied the effects of antenatal anxiety into childhood. High levels of maternal anxiety, at 32 weeks postmenstrual age (pma), doubled the risk for hyperactivity and inattention problems, conduct disorder, and emotional problems at the ages of 47 and 81 months in both boys and girls. Maternal anxiety at 18 weeks pma affected total behavioral and emotional problems, but only in girls. This study relied on a short mother report screening instrument in which each of the three problem scales was typically defined by five items. Four research groups found effects on various behavioral outcomes at earlier postnatal ages. Van den Bergh, Vandenberghe, Daniels, Casaer, and Marcoen (1989; $N = 70$) found that antenatal anxiety explained 10% to 25% of the variance in neonatal movements and behavioral states in hyperactivity, frequent crying, sleeping and feeding difficulties, and difficult temperament during the first 7 months of life. Associations were stronger for anxiety at 12 to 22 weeks pma than for anxiety at 23 to 31 and 32 to 40 weeks pma (Van den Bergh, 1989, 1990, 1992). In their study, Huizink, Robles de Medina, Mulder, Visser, and Buitelaar (2002, 2003; $N = 170$) perceived stress and pregnancy-related anxieties at 15 to 17 weeks pma, and at 27 to 28 weeks pma showed the strongest effects on difficult temperament at 3 months and attention regulation and mental and motor development at 3 and 8 months, whereas at 37 to 38 weeks pma early morning cortisol levels had a smaller effect. In Brouwers, van Baar, and Pop (2001, $N = 105$) maternal anxiety was measured at 32 weeks pma and was significantly related to observer report measures of attention at 3 weeks and 12 months of age, as well as to mental development at 24 months of age. Wadhwa and colleagues (Wadhwa et al., 2002; Wadhwa, Sandman, & Garite, 2001) mentioned that in samples of 24 to 49 mother–infant dyads, maternal stress and stress hormones during pregnancy had an effect on difficult temperament in children up to 3 years of age. In all of these studies, the associations were found after accounting for confounding variables, such as smoking during pregnancy, birth weight, socioeconomic class, and postnatal maternal anxiety or depression. We can conclude that, across the five studies, the effects found are not confined to a specific gestational period nor are they highly specific. However, the observation in two of the studies, that the associations were strongest for early- and mid-gestation anxiety, concur with findings of experimental studies with nonhuman primates (Schneider, Moore, Kraemer, Robert, & DeJesus, 2002; Schneider, Roughton, Koehler, & Lubach, 1999), and the evidence for a link with antenatal anxiety is most conclusive for hyperactivity, inattention problems, and difficult temperament. Differences in the results of the five studies might be due to differences in: (a) the exact timing of the anxiety measurements, the period to which they refer, the intensity of anxiety and the actual persistence of anxiety throughout pregnancy; (b) the scales used to measure the independent and dependent variables; (c) biological, psychological, and environmental factors in prenatal and postnatal life period controlled for (covariates) and not controlled for; and (d) genetic differences (Heron, O’Connor, Evans, Golding, & Glover, 2004; Kofman, 2002; Mulder et al., 2002).

How can the results of the studies cited be explained? At this point we would like to introduce the fetal programming hypothesis (or, more generally, perinatal programming hypothesis), which is derived from human epidemiologic and animal model data. As extensively explained by O’Connor (2003), this hypothesis “suggests a complementary and perhaps competing perspective to predominant developmental theories explaining effects of early experiences on later psychological development” (O’Connor et al., 2003, p. 1034). The fetal programming hypothesis states that when disturbing factors act during specific sensitive periods of development, they exercise organizational effects—or program
some set points—in a variety of systems (e.g., metabolic, cardiovascular, or immune system) by different underlying mechanisms (Barker, 1998, 2002; Coe, Lubach, & Karaszweski, 1999; Nathanielsz, 1999). Problems will arise if the environment changes later in life. The organism is then hampered because the programmed set points do not readily readapt to the new environment. The malleability or adaptive plasticity of biological systems is developmentally constrained, and this produces maladaptive physiology and ultimately predisposes to disease or disorder (Welberg & Seckl, 2001). For example, when the body’s capacity to metabolize glucose was set according to nutritionally deprived circumstances during prenatal life, the body is unable to adjust when dramatic improvements in the nutritional environment occur after birth, and diabetes results (Barker, 1998). The hypothalamic-pituitary-adrenocortical (HPA) axis is particularly susceptible to perinatal programming by glucocorticoids, at least in rodents. Antenatally stressed animals show prolonged endocrinologic stress responses, as well as behavioral symptoms related to dysregulation of the HPA axis, such as anxiety, fearfulness and maladaptive coping in novel or stressful situations, high stress responsivity, declined attention and impaired learning or memory, and neuromotor delays. Associated neurochemical changes in limbic areas include reduced glucocorticoid receptor expression in the hippocampus and elevated expression of corticotropin releasing hormone (CRH) in the amygdala. Programming of developing neurotransmitter systems, for example, of the monoaminergic (i.e., noradrenergic, dopaminergic, and serotonergic) system, which is functionally related to the HPA axis, may also contribute to the observed changes. Disturbance in HPA axis regulation and brain monoamine levels are associated with several disorders in humans (Herlenius & Lagercrantz, 2001; Herman et al., 2003; Huizink, Mulder, & Buitelaar, 2004; Ladd et al., 2000; Maccari et al., 2003; Weinstock, 2001; Welberg & Seckl, 2001).

Research Aim

The present study represents the second wave of the study of Van den Bergh and colleagues and investigates whether high maternal anxiety during pregnancy enhances the offspring’s susceptibility for childhood disorders and whether specific vulnerable periods exist. Mothers completed the State Trait Anxiety Inventory (STAI) at 12 to 22, 23 to 31, and 32 to 40 weeks pma. Clinical questionnaires and an observation scale on ADHD and externalizing and internalizing problems in the 8- and 9-year-old child were completed by the mother and the child, and by the child’s teacher and an external observer, both blinded to the level of maternal anxiety during pregnancy. Potential confounders were taken into account, namely, gender of the child, parents’ educational level, smoking during pregnancy, birth weight for pma, and maternal postnatal anxiety. The findings of this study might bring indirect evidence for the fetal programming hypothesis and might contribute to the knowledge of early origins of childhood disorders.

Method

Participants

Of the 86 women that participated at the start of the study, 71 participated in the second wave, together with their 8- and 9-year-old firstborns, 38 boys and 34 girls (2 girls were twins), with a mean age of 8 years 6 months. Eligibility criteria at the start of the study were that the women should be Caucasian, Dutch speaking, between the ages of 18 and 30, not yet have given birth to a viable child, between 12 and 22 weeks pregnant, without obstetrical complications or medical risks, and not using drugs or medication with risks to the fetus. To recruit the sample, the first author approached eligible women about volunteering for the study while at the Obstetrical and Gynecological Board consultations of the University Hospital Gasthuisberg in Leuven. The ethical committee for experiments on human beings of the Catholic University of Leuven approved the study. All participants gave their informed consent.

Sociodemographic, psychiatric, and obstetric data were collected in an interview and by medical chart review. Although there was variation in the sociodemographic characteristics, the sample mainly consisted of healthy, well-educated women, 94% of whom were married. The following four levels of education were achieved by the parents: without high school diploma (mothers = 13.8%, fathers = 9.2%), high school graduate without additional schooling (mothers = 25.1%, fathers = 33.8%), additional schooling beyond high school (mothers = 30.8%, fathers = 12.3%), and university degree (mothers = 32.3%, fathers = 44.6%). None of the women had a psychiatric disorder or had ever been treated for a primary anxiety disorder. All pregnancies were dated using the last menstrual period or a sonographic examination before 20 weeks if dates had been uncertain. All babies were delivered in the hospital between 36 and 41 weeks pma with a mean
birth weight of 3301.48 g ($SD = 490.68$), had 5-min APGAR scores of 9 or 10 (2 babies with score 8) and scored high on Prechtl’s list of 52 optimal obstetrical conditions ($M = 45.6, SD = 2.9$; Michaeûlis, Dopfer, Gerbig, Dopfer-Feller, & Rohr, 1979).

**Study Design**

The participants were included in a prospective follow-up study with six assessments in the first wave, at 12 to 22, 23 to 31, and 32 to 40 weeks pma, and at 1, 10, and 28 weeks after birth. In Wave 1 a standardized continuous observation, which lasted 100 to 120 min, was made of behavioral states and movements at 36 to 38 weeks pma with ultrasound and cardiography, as well as at the fifth or sixth day after birth (for a complete description of Wave 1, see Van den Bergh, 1989, 1990, 1992). In Wave 2 during a home visit that lasted 90 to 120 min, a female observer, blinded to the level of maternal anxiety during pregnancy, interviewed the mother and assisted the child in completing standardized questionnaires. She also collected completed questionnaires that had been sent to the mother before the home visit. Questionnaires were sent with the child to his or her teacher, who sent the completed questionnaire back in a prepaid envelope.

**Instruments and Measures**

**Maternal Anxiety**

The anxiety of the mother was measured using a Dutch version (Van der Ploeg, Defares, & Spielberger, 1980) of the STAI, which is a self-report questionnaire consisting of two subscales of 20 items, scored from 1 to 4. State anxiety is conceptualized as a transient emotional condition, characterized by subjectively experienced tension, together with an enhanced activity of the autonomous nervous system. Trait anxiety reflects a disposition indicating anxiety proneness. Cronbach’s alphas are .95 and .93 for state and trait anxiety scales, respectively (Van der Ploeg et al., 1980), and in our sample exceeded .90 across assessments. STAI data were available at all six occasions in Wave 1 and at Wave 2. State anxiety measures provide a valid indication of change in the intensity of transitory anxiety in response to real-life stress (Spielberger, 1975). Therefore, state (and not trait) anxiety measures were included as predictors in our models investigating the effects of antenatal maternal anxiety. The analyses focused on state anxiety at 12 to 22 weeks pma (Anx 12–22 weeks pma) and state anxiety at 32 to 40 weeks pma (Anx 32–40 pma). Anx 23–31 weeks pma ($M = 34.94, SD = 8.79$) was significantly lower than Anx 12–22 weeks pma ($t = 3.17, p = .00$) and lower than Anx 32–40 weeks pma ($t = 1.56, p = .12$), rendering the possibility of midgestation anxiety having a less plausible effect in comparison with Anx 12–12 weeks pma or Anx 32–40 weeks pma. It also turned out that correlations of Anx 23–31 weeks pma with the final dependent variables were non-significant ($ps > .05$).

The trait anxiety subscale measures dispositional anxiety or anxiety in general. Women with high anxiety levels were expected to differ from those with low anxiety levels in postnatal contact with their child and in caregiving. We controlled for this potential confounding effect by including a postnatal trait anxiety measure in our model. A principal component analysis (PCA) conducted on all postnatal trait anxiety measures (1, 10, and 28 weeks, and 8–9 years), revealed one component explaining 65% of the variance. A variable consisting of the standardized component score for each mother was used as a covariate in the analyses.

**Socioeconomic Status: Parents’ Educational Level**

Maternal and paternal education was coded on a 4-point scale (1 = without high school diploma, 2 = high school graduate without additional schooling, 3 = additional schooling beyond high school, 4 = university degree). A PCA conducted on both scores yielded one component explaining 85% of the variance.

**Obstetric and Antenatal Risk: Smoking During Pregnancy and Birth Weight**

Two prenatal covariates likely to be related to the children’s behavioral and emotional outcomes were included in the statistical analyses: amount of cigarettes smoked daily during pregnancy, where 0 = not smoking ($n = 54$) and 1 = smoking ($n = 18$; 13 smoking less than 5, 3 smoking 10, 1 smoking 15, and 1 smoking 25 cigarettes), and birth weight for pma. The confounding influence of other obstetric and antenatal risk factors (e.g., pregnancy complications, parity, medication use) was avoided by using strict eligibility criteria when recruiting the sample.

**Outcome Measures: Cross-Informant Composites of Specific Childhood Disorders**

To obtain robust outcome measures for ADHD symptoms and externalizing and internalizing problems, composite measures were constructed by conducting PCAs on scales of self-administered
clinical questionnaires and standardized observation scales completed by mother, teacher, observer, or child. Standardized Dutch versions of the scales were used; all Cronbach’s alphas were between .78 and .86 in our sample.

**Mother and teacher report measures.** From the Child Behavior Checklist (CBCL/4–18 years; Verhulst, van der Ende, & Koot, 1996) and the Teacher’s Report Form (TRF/4–18 years; Verhulst, van der Ende, & Koot, 1997), two widely used clinical standardized formats (120 items scored from 0 to 2) for reporting behavioral problems and competencies of children ages 4 to 18, we used the Attention Problems scale as a measure for ADHD symptoms and the broadband dimensions of Externalizing and Internalizing Problems. The Externalizing Problems Scale is composed of the Aggressive Behavior and Delinquent Behavior subscales. The Internalizing Problems Scale is composed of the Anxious/Depressed, Somatic Complaints, and Withdrawn subscales. Scores are reported in the form of T scores (M = 50, SD = 10). On all small-band scales of CBCL and TRF, including the Attention Problem Scale, T scores above 70 are considered to be clinically significant and T scores between 67 and 70 are considered borderline. For Externalizing and Internalizing Problems, T scores above 63 are clinically significant and T scores between 60 and 63 indicate borderline pathology. From the Conners Abbreviated Teacher Rating Scale (CATRS; Bloë & Curfs, 1986), a 4-point scoring scale for measuring ADHD symptoms, we obtained measures for two clusters: (a) hyperactivity/inattention (four items; e.g., “is restless and overactive” “is easily distracted”) and (b) acting-out behavior (five items; e.g., “disturbing behavior towards other children” “has temper tantrums”). A score above 16 on the total scale and agreement between parent and teacher regarding symptoms of inattention/hyperactivity indicate pervasive symptoms for ADHD (van der Meere, Shalev, Börger, & Gross-Tsur, 1995).

**Observer report measure.** The Groninger Behavior Observation Scale (GBO; Kalverboer, 1990) consists of 12 behavior descriptions, scored from 1 to 4, indicating attention and hyperactivity problems (e.g., “easily gives up” “makes a lot of unnecessary movements during the execution of the task”). As children with ADHD are most problematic in their behavior in a context involving task-directed persistence and behavioral restraint (Barkley, 2003), we asked an external observer to administer scales to the child during the home visit and to observe his or her behavior while completing the scales.

**Child report measure.** The State Trait Anxiety Scale for Children (STAIC; Bakker, Van Wieringen, Van der Ploeg, & Spielberger, 1989), a 3-point anxiety scale, with 20 items measuring state anxiety and 20 items measuring trait anxiety, was completed by the child during the home visit.

**Composites.** Four composites were constructed: (a) ADHD symptoms—a PCA on mother and teacher report scales Attentional Problems (CBCL/TRF) and Hyperactivity/Inattention (CATRS) and on external observer report scale (GBO) revealed one component that explained 66% of the variance; (b) externalizing problems—a PCA on mother and teacher report scales Externalizing Problems (CBCL/TRF) and Acting-Out (CATRS) resulted in one component that explained 66% of the variance; (c) internalizing problems—a PCA on mother and teacher report scales Internalizing Problems (CBCL/TRF) and self-report anxiety scales (STAIC) did not reveal one component; therefore, a PCA was conducted on mother and teacher scales Internalizing Problems (CBCL/TRF) separately, which revealed one component that explained 65% of the variance; and (d) self-report anxiety—a PCA on the two scales of the STAIC revealed one component that explained 71% of the variance.

**Data Analysis**

We had complete data sets for 52 children. The data for the remaining 20 children were partially missing at random, resulting in 10.9% of all data that were missing, most of which were teacher and mother report measures. Observer and child report data were complete, except for 1 child. The values of the missing data were estimated through expectation maximization (EM) algorithm for maximum likelihood (ML) estimation as provided in SPSS (version 11). EM was based on all available data observed in Wave 2. In handling missing data, imputation techniques are preferred over case deletion because retaining the full sample helps prevent loss of power resulting from diminished sample size. Imputation makes more efficient use of the observed data—no cases are sacrificed—and the apparently complete data set can be analyzed by standard methods, whereas case deletion may induce bias (Schafer & Graham, 2002; Wothke, 2000).

Four hierarchical regressions were performed on the outcome measures. Five covariates (gender of the child, parents’ educational level, smoking during pregnancy, birth weight, and postnatal maternal trait anxiety) were entered in the first step, and two predictors (Anx 12–22 weeks pma and Anx 32–40 weeks pma) were entered in the second step. Interactions between gender (coded as 0 = boys, 1 = girls)
and each of the predictors were entered in a third step. Because none of the interactions turned out to be significant in any of the models, they were removed in all final models. This approach gave an indication of the unique contribution of the anxiety predictors in predicting childhood disorders. Two cases were removed in the regression model for externalizing problems. Based on their studentized residuals (> 2.65) they were identified as outliers by SPSS (see Fox, 1997). When conducting analyses on the 52 children with complete data, the proportion of the variances explained by the predictors was slightly higher (about 2%) than in analyses on the whole sample.

Multicollinearity can pose serious threats to the interpretation of regression coefficients as indexes of effects. To mitigate this problem we controlled for the tolerance coefficient. In all analyses the tolerance coefficient of covariates and predictors was between 64% and 95%, indicating that between 64% and 95% of the explained variance was independent of the variance explained by other variables. An alpha level of .05 was used for all statistical tests.

Results

Descriptive Analyses

Table 1 shows the descriptive statistics of and correlations among predictors, covariates, and dependent variables. Maternal anxiety scores in our sample covered the range of scores observed in a nonclinical female Dutch community sample (Van der Ploeg et al., 1980). The means of Anx 12–22 weeks pma and 32–40 weeks pma were situated, respectively, at Decile 6 and Decile 5 of the Dutch

Table 1
Descriptives and Intercorrelations of Predictors, Covariates and Dependent Variables (N = 72)

<table>
<thead>
<tr>
<th>Variable</th>
<th>M</th>
<th>SD</th>
<th>Range</th>
<th>2</th>
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<tbody>
<tr>
<td>Predictors</td>
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<tr>
<td>1. Anx 12–22 weeks pma</td>
<td>38.70</td>
<td>7.75</td>
<td>24.00 to 59</td>
<td>.25*</td>
<td>-.09</td>
<td>.06</td>
<td>-.07</td>
<td>.31**</td>
<td>.51***</td>
<td>.42***</td>
<td>.18</td>
<td>.23†</td>
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<tr>
<td>2. Anx 32–40 weeks pma</td>
<td>36.14</td>
<td>8.79</td>
<td>20.00 to 58.00</td>
<td>-</td>
<td>-.33**</td>
<td>.21</td>
<td>-.17</td>
<td>.57***</td>
<td>.02</td>
<td>.22†</td>
<td>.28*</td>
<td>-.10</td>
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<td>Covariates</td>
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<td>3. Parents’ educational level</td>
<td>1</td>
<td>0</td>
<td>-2.21 to 1.69</td>
<td>-</td>
<td>.07</td>
<td>-.06</td>
<td>-.50</td>
<td>-.19</td>
<td>-.03</td>
<td>-.16</td>
<td>-.06</td>
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<td>4. Smoking in pregnancy</td>
<td>1.42</td>
<td>0</td>
<td>0 to 25</td>
<td>-</td>
<td>-.28*</td>
<td>.22</td>
<td>.04</td>
<td>.05</td>
<td>-.03</td>
<td>.06</td>
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<tr>
<td>5. Child’s birth weight</td>
<td>33.01</td>
<td>4.68</td>
<td>2245 to 4220</td>
<td>-</td>
<td>-.14</td>
<td>-.10</td>
<td>.05</td>
<td>.06</td>
<td>-.15</td>
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<tr>
<td>6. Postnatal trait anxiety</td>
<td>1</td>
<td>0</td>
<td>-2.09 to 2.24</td>
<td>-</td>
<td>.13</td>
<td>.14</td>
<td>.27*</td>
<td>-.01</td>
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<td>Dependent variables</td>
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<tr>
<td>7. C ADHD symptoms</td>
<td>1.36</td>
<td>2.91</td>
<td>0 to 11</td>
<td>-</td>
<td>.68**</td>
<td>.35**</td>
<td>.15</td>
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<tr>
<td>Attention problems CBCL</td>
<td>5.09</td>
<td>5.59</td>
<td>0 to 27</td>
<td>-</td>
<td>.45</td>
<td>.32</td>
<td>.27</td>
<td>.30</td>
<td>.33**</td>
<td>.11</td>
<td></td>
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<tr>
<td>Attention problems TRF</td>
<td>7.34</td>
<td>2.80</td>
<td>4 to 15</td>
<td>-</td>
<td>.34</td>
<td>.28</td>
<td>.21</td>
<td>.18</td>
<td>.12</td>
<td>.10</td>
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<tr>
<td>Hyper/inatt CATRS Mo</td>
<td>6.08</td>
<td>2.35</td>
<td>4 to 14</td>
<td>-</td>
<td>.33</td>
<td>.27</td>
<td>.21</td>
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<td>Hyper/inatt CATRS Te</td>
<td>22.26</td>
<td>6.18</td>
<td>15 to 39</td>
<td>-</td>
<td>.68**</td>
<td>.35**</td>
<td>.15</td>
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<td>GBO observer</td>
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<td>8. C externalizing problems</td>
<td>1</td>
<td>0</td>
<td>-1.19 to 3.70</td>
<td>-</td>
<td>.33**</td>
<td>.11</td>
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<tr>
<td>Externalizing CBCL</td>
<td>7.53</td>
<td>5.70</td>
<td>0 to 24</td>
<td>-</td>
<td>.33**</td>
<td>.11</td>
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<tr>
<td>Externalizing TRF</td>
<td>4.58</td>
<td>7.28</td>
<td>0 to 38</td>
<td>-</td>
<td>.33**</td>
<td>.11</td>
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<tr>
<td>Acting-out CATRS Mo</td>
<td>7.90</td>
<td>2.43</td>
<td>5 to 18</td>
<td>-</td>
<td>.33**</td>
<td>.11</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Acting-out CATRS Te</td>
<td>5.45</td>
<td>1.68</td>
<td>4 to 11</td>
<td>-</td>
<td>.33**</td>
<td>.11</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. C internalizing problems</td>
<td>1</td>
<td>0</td>
<td>-1.31 to 2.94</td>
<td>-</td>
<td>.10</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Internalizing CBCL</td>
<td>7.01</td>
<td>5.02</td>
<td>0 to 21</td>
<td>-</td>
<td>.33**</td>
<td>.11</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Internalizing TRF</td>
<td>4.72</td>
<td>4.24</td>
<td>0 to 21</td>
<td>-</td>
<td>.33**</td>
<td>.11</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10. C self-report anxiety</td>
<td>1</td>
<td>0</td>
<td>-2.51 to 2.72</td>
<td>-</td>
<td>.10</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>State anxiety STAIC</td>
<td>29.60</td>
<td>4.32</td>
<td>20 to 45</td>
<td>-</td>
<td>.10</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trait anxiety STAIC</td>
<td>32.75</td>
<td>6.31</td>
<td>20 to 48</td>
<td>-</td>
<td>.10</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Note. Anx = maternal state anxiety; pma = postmenstrual age; C = component resulting from principal component analysis; ADHD = attention deficit hyperactivity disorder; CBCL = Child Behavior Checklist; TRF = Teacher’s Report Form; Hyper/inatt = hyperactivity/inattention; CATRS = Conners Abbreviated Teacher Rating Scale; Mo = mother; Te = teacher; GBO = Groninger Behavior Observation Scale; STAIC = State Trait Anxiety Scale for Children.

†p<.10. *p<.05. **p<.01. ***p<.001.
sample, indicating that the mean level of Anx 12–22 weeks pma in our sample was slightly higher than the level of anxiety in normal, nonpregnant women. Anx 12–22 weeks pma was significantly higher than Anx 32–40 weeks pma ($t = 2.11, p = .039$). In early gestation, 40% of the women scored between 40 and 59 on Anx 12–22 weeks pma; in late gestation 29% of the women scored similarly on Anx 32–40 weeks pma. It is interesting to note that mothers of boys ($M = 40.42, SD = 8.38$) scored higher on Anx 12–22 weeks pma than did mothers of girls ($M = 36.77, SD = 6.57$), $t(72) = 2.043, p = .045$. Of the women who scored above the 75th percentile (score = 43) on Anx 12–22 weeks pma, 11 were carrying a boy, and 5 were carrying a girl.

For 11.11% of the children (6 boys, 2 girls) on either CBCL or TRF, scores concerning attention problems indicated at least borderline pathology and 6.94% had clinical problems. On the CATRS, 9.7% met the criteria for pervasive ADHD symptoms, and when combining CBCL, TRF, and CATRS data, 14% (7 boys, 3 girls) exhibited clinical ADHD symptoms. For externalizing problems, 9.3% (TRF) to 14.8% (CBCL) of the children showed at least borderline pathology, and between 6.9% (CBCL) and 7.4% (TRF) scored in the clinical range. For internalizing problems, 9.3% (TRF) to 24.1% (CBCL) of the children showed at least borderline pathology, and between 5.6% (TRF) and 14.8% (CBCL) had clinical problems.

The prenatal and postnatal maternal anxiety measures were significantly correlated. Correlations with and between the covariates showed that Anx 32–40 weeks pma was negatively correlated with parents’ educational level, that smoking during pregnancy and child’s birth weight were negatively correlated, and that postnatal maternal trait anxiety was correlated with internalizing problems of the child. All dependent variables but self-report anxiety were significantly intercorrelated.

### Table 2

**Summary of Hierarchical Regression Analysis Predicting Childhood Disorders in 8- and 9-Year-Olds (N = 72)**

<table>
<thead>
<tr>
<th>Childhood disorders</th>
<th>C ADHD symptoms</th>
<th>C externalizing problems*</th>
<th>C internalizing problems</th>
<th>C self-report anxiety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Covariates and predictors</td>
<td>$\beta$</td>
<td>SE $\beta$</td>
<td>$\beta$</td>
<td>SE $\beta$</td>
</tr>
<tr>
<td>Step 1: Covariates</td>
<td>Gender child</td>
<td>$-0.22^*$</td>
<td>$0.21$</td>
<td>$-0.03$</td>
</tr>
<tr>
<td>Parents’ educational level</td>
<td>$-0.20$</td>
<td>$0.10$</td>
<td>$0.07$</td>
<td>$0.10$</td>
</tr>
<tr>
<td>Smoking in pregnancy</td>
<td>$0.07$</td>
<td>$0.23$</td>
<td>$0.24^*$</td>
<td>$0.24$</td>
</tr>
<tr>
<td>Birth weight child</td>
<td>$-0.13$</td>
<td>$0.10$</td>
<td>$0.24^*$</td>
<td>$0.11$</td>
</tr>
<tr>
<td>Postnatal trait anxiety</td>
<td>$0.05$</td>
<td>$0.13$</td>
<td>$-0.11$</td>
<td>$0.13$</td>
</tr>
<tr>
<td>$R^2$ for Step 1</td>
<td>.15</td>
<td>.13</td>
<td>.11</td>
<td>.10</td>
</tr>
<tr>
<td>Step 2: Predictors</td>
<td>Anx 12–22 weeks pma</td>
<td>$0.48^{***}$</td>
<td>$0.01$</td>
<td>$0.36^{**}$</td>
</tr>
<tr>
<td>Anx 32–40 weeks pma</td>
<td>$-0.25$</td>
<td>$0.02$</td>
<td>$0.20$</td>
<td>$0.02$</td>
</tr>
<tr>
<td>$\Delta R^2$ for Step 2</td>
<td>$0.22^{***}$</td>
<td>$0.15^{**}$</td>
<td>$0.02$</td>
<td>$0.09^*$</td>
</tr>
<tr>
<td>$F_{Model}$</td>
<td>$5.47^{***}$</td>
<td>$3.40^{**}$</td>
<td>$1.0$</td>
<td>$1.39$</td>
</tr>
</tbody>
</table>

Note. ADHD = attention deficit hyperactivity disorder; Anx = maternal state anxiety; pma = postmenstrual age; C = component resulting from principal component analysis.

*a $n = 70$; two outliers were dropped.

*p < .05. **$p < .01$. ***$p < .001$. 

### Maternal Anxiety During Pregnancy and Childhood Disorders at Ages 8 and 9

Results of the multiple hierarchical regressions (see Table 2) revealed that, even after controlling for child’s gender, parents’ educational level, smoking, birth weight, and postnatal maternal anxiety, prenatal maternal anxiety was significantly associated with ADHD symptoms, externalizing problems, and self-report anxiety in the 8- and 9-year-old offspring. The proportion of the variance explained uniquely by the predictors was significant (22%, 15%, and 9%, respectively). In our sample, Anx 12–22 weeks pma was a significant independent predictor of these disorders; this was not the case for Anx 32–40 weeks pma. No significant associations with maternal anxiety during pregnancy emerged in the multiple regression for internalizing problems, despite a significant correlation of Anx 32–40 weeks pma (see...
The present study shows that a high level of maternal state anxiety during pregnancy enhances the offspring’s susceptibility for developing a childhood disorder. Even after controlling for the child’s gender, parents’ educational level, birth weight, smoking during pregnancy, and postnatal maternal anxiety, maternal state anxiety during pregnancy explained between 9% and 22% of the variance in the childhood disorders investigated. The level of Anx 12–22 weeks pma was slightly higher than the state anxiety level in a normal, nonclinical sample, and significantly higher than Anx 32–40 weeks pma. In contrast to Anx 32–40 weeks pma, Anx 12–22 weeks pma turned out to be a significant independent predictor of three of the four childhood disorders studied. This result at least suggests that the period between 12 and 22 weeks pma is a vulnerable period for developing cross-situational ADHD symptoms, externalizing problems, and anxiety during childhood. However, it cannot be excluded that the vulnerability period starts even before 12 weeks pma or covers only a subperiod of the 12- to 22-week pma period, or that other measures of anxiety (e.g., of pregnancy related anxiety) or higher levels of late gestation state anxiety than those observed in the present sample, might enhance the susceptibility for the childhood disorders investigated. The results of the present study strengthen the evidence established in the five prospective studies mentioned in the Introduction for the association between high levels of maternal anxiety during pregnancy and behavioral, emotional, and cognitive problems in infancy and childhood. In what follows these results are discussed in the framework of the fetal programming hypothesis and a few strengths, limitations, and implications of the present study are briefly described.

The Fetal Programming Hypothesis Perspective

Fetal programming reflects the action of a disturbing factor during sensitive periods of development to exercise organizational effects that constrain the malleability of biological systems and ultimately predispose to disorder (Seckl, 2001). The results of our study are consistent with a fetal programming hypothesis in at least two ways.

First, evidence is found in the timing of antenatal maternal anxiety enhancing childhood disorder susceptibility. Between 12 and 22 weeks pma, the brain is susceptible to programming because many areas are undergoing active growth and neurons are still immature (Welberg & Seckl, 2001); that is, the cascade of orderly timed processes of neuron proliferation; migration; early differentiation; and, sometimes, cell death is taking place. Although region-by-region differences exist in the exact time course of these processes, in humans most cerebral cortex neurons are generated and have at least started their migration between Embryonic Days 40 and 125 (ca 8–20 weeks pma or 6–18 weeks after conception; Levitt, 2003; Nowakowski & Hayes, 2002; Rakic, 2002a, 2002b). For example, the limbic system (e.g., the hippocampus, amygdala) and limbic regions of the cortex (e.g., anterior cingulate cortex [ACC]) start differentiating already in the 3rd month of gestation, and the neocortex starts only in the 6th month (Johnson, 1997). Neurogenesis, neuronal migration, and differentiation are controlled by processes intrinsic to the cell and processes extrinsic to the cell, that is, by genes and their products, by interactions between cells, and by interactions of cells with early neurotransmitters and neuromodulators acting as growth factors (Nowakowski & Hayes, 2002). It is important to note that although before midgestation these developmental processes are not driven by activity that is modulated by sensory input, they nevertheless can be altered (Bourgeois, 1997). This happens when environmental factors modulate the influence of intracellular and extracellular developmental signals (Herlenius & Lagercrantz, 2001; Levitt, Reinoso, & Jones, 1998; Weaver et al., 2001). In general, the earlier the disturbance occurs, the greater is its potential influence on subsequently occurring events and maturing and, finally, on the mature structure–function relationship (Nowakowski & Hayes, 2002). If, for instance, in the 3rd or 4th month of gestation, a teratogen modulates the influence of other developmental signals and disrupts neuronal migration, this may result in abnormality in cell position, which may alter the laminar structure of the ACC. During the onset of differentiation, disturbances by teratogens such as glucocorticoids (cortisol in humans) can, for example, influence the growth of dendrites, disturb the timetable of the expression of several neurotransmitter phenotype (e.g., of the monoaminergic system) and neuropeptides (e.g., CRH) and their receptors and alter the receptor sensitivity, which...
finally alters the balance between excitatory and inhibitory brain circuits (Ladd et al., 2000; Schneider et al., 1998; Weaver et al., 2001; Weinstock, 2001).

In humans, subtle aberrations in neuronal migration and early differentiation may play a role in disorders such as ADHD, dyslexia, epilepsy, autism, and some forms of schizophrenia (see Fernandez-Duque & Posner, 2001; Monk, Webb, & Nelson, 2001; Nowakowski & Hayes, 2002). It is postulated that in general the disturbance of the particular developmental processes taking place in specific brain areas at the time of the prenatal insult, in interaction with the genetic susceptibility of the offspring and mediated by later prenatal and postnatal environmental factors, will determine the way perceptual, cognitive, motor, arousal, and emotional processes are integrated, thereby influencing the kind of disorder the child might develop (Grossman et al., 2003; Ladd et al., 2000). For instance, it is known that the ACC, in which dopamine, noradrenaline, and CRH are present in abundance, plays an important role in self-regulation by integrating functions of cortical and subcortical areas such as attention, executive functioning, motor control, drive, arousal regulation, awareness of emotions, and subjective distress (Damasio, 1998; Paus, 2001, Posner & Raichle, 1994). To our opinion, results of at least two studies make it plausible that alteration of ACC structure–function relationships, caused by early teratogens, may have an etiological role in the development of childhood disorder observed in our study. First, in humans, with a diagnosis of bipolar disorders or schizophrenia, a change in the density of neurons in particular layers of the ACC has been verified in postmortem cases (Benes, Vincent, & Todtenkopf, 2001). Second, in rabbits early prenatal exposure to cocaine led to anomalous dendritic development of ACC neurons, causing impairment of attentional processes (Stanwood & Levitt, 2004). Observation with functional magnetic resonance imaging of the differential patterns of activation of cortical and subcortical areas in children with and without ADHD (e.g., Durston et al., 2003; Rubia, 2002) at least concur with a hypothesized role of ACC structure–function relationships in ADHD. However, longitudinal studies linking the patterns of activation to prenatal programming are lacking. Mayes (2000, 2002) developed a multilevel gate model in which the impaired self-regulation of children prenatally exposed to cocaine is understood as an imbalance between and within dopaminergic and noradrenergic systems in cortical and subcortical areas. She hypothesized that the threshold for switching between more executive (prefrontal) and more automatic (posterior frontal and subcortical) modes of functioning may be permanently altered as a result of fetal programming by prenatal cocaine exposure and other early stressful experiences. In the same line, we tentatively hypothesized that in our sample, in children of highly anxious women, monoaminergic brain circuits (and the HPA axis and limbic system) may have been prenatally programmed by the disturbing influence of anxiety-related hormones between 12 and 22 weeks pma. ADHD symptoms (inattention, impulsivity, disinhibition, hyperactivity), externalizing behavior (conduct disorders, aggression), and self-report anxiety (emotional inhibition and lability, high subjective distress in novel situations) may be seen as different developmental progressive forms of early impaired self-regulation (cf. Posner & Rothbart, 2000; Rubia, 2002).

A second source of evidence for the programming hypothesis is generated when combining the results of both waves of our study. A strength of the first wave of our study was that, based on the results of a pilot study (Van den Bergh, Mulder, et al., 1989), we started to observe the effects of maternal anxiety already in the prenatal life period. Pad models showed that the effect of antenatal maternal anxiety on fetal general movements and length of quiet sleep periods at 36 to 38 weeks pma was reflected in comparable behavioral measures at Days 5 to 6 after birth. Neonatal maternal anxiety had no direct effect on these measures (Van den Bergh, 1989, 1990). Clearly, these analyses suggest that maternal emotions affect fetal neurobehavioral development, altering the developmental trajectory from prenatal life onward. Moreover, the proportion of variance explained by antenatal maternal anxiety was stronger than the proportion explained by postnatal maternal anxiety and did not change from between 36 to 38 weeks pma and 8 to and 9 years after birth. These results all are consistent with a fetal programming hypothesis.

Strengths and Limitations of the Study

First, one strength of our study is the prospective design with a retention rate of 84% in the second wave, over about 9 years. Second, maternal anxiety was measured repeatedly during gestational periods that are assumed to be critical windows for brain development and at different postnatal periods. The range of anxiety in a normal, nonclinical population was covered in our sample, and a substantial proportion of the women scored in the higher range. Third, robust cross-informant measures of childhood disorders, based on standardized clinical scales and an observation scale, were used. This robustness
makes our results difficult to explain by a simple rater bias explanation.

Some limitations and weaknesses of the study must be mentioned. First, the sample was relatively small and the results might be sample specific. Second, the inclusion of physiological measures (e.g., the level of cortisol in the mother) would have enabled us to test their assumed causative role in fetal programming. Third, our design was not genetic sensitive. It is, however, unlikely that the associations we found can be explained by genetic mediation only because this does not explain why the associations established in our sample specifically involve prenatal maternal anxiety and not postnatal anxiety (cf. O’Connor et al., 2002; O’Connor et al., 2003). Of course, it is plausible that highly anxious mothers are carrying genes for ADHD and that physiological events involved in high antenatal maternal anxiety trigger gene regulatory mechanisms and the expression of ADHD genes in the offspring. If this were the case, it would only underline the importance of this prenatal environmental factor (Gottlieb & Halpern, 2002; Grossman et al., 2003; Rutter, Silberg, O’Connor, & Simonoff, 1999).

Implications and Future Research

The present study yielded some of the strongest indirect evidence available today that antenatal maternal anxiety may contribute to the shaping of alteration in the child’s neurobehavioral development—and, hence, enhance the susceptibility for childhood disorders—by programming some set points in early developing brain structure–function relationships. Clearly, many questions on exactly how fetal programming works in humans, and in what ways the timing, kind, and duration of environmental disturbances are finally related to altered neurobehavioral development, are still unresolved. For example, how can the intriguing links among early gestation maternal anxiety, gender of the offspring, and incidence of ADHD found in our sample be explained? Are mothers of male fetuses more anxious because boys introduce testosterone and corresponding physiological changes into their mother’s body? Do these changes enhance feelings of anxiety and concomitant release of hormones (e.g., cortisol) in the mother? Is it the interaction between testosterone and cortisol (McEwen, 2000; Weinstock, 2001) that explains the higher incidence of ADHD in boys than in girls?

We agree with O’Connor et al. (2003, p. 1034) that, theoretically, fetal programming offers a complementary and perhaps competing perspective to the predominant theories of development and psychopathology. Converging evidence from other studies in identifying specific programming windows during gestation could give the impetus to develop prevention, intervention, and support programs for highly anxious pregnant women. These programs could include stress-reduction instructions (e.g., Urizar et al., in press) and cognitive–behavioral treatments to reduce anxiety and neuroendocrine reactions to stress from early gestation on, or even before conception (e.g., Facchinetti, Tarabusi, & Volpe, 2004). They may not only benefit the mother but also the child to be born.

In the future, we plan to investigate the long-lasting effects of prenatal maternal anxiety. When the children are 14 and 15 years old, temperament, behavioral, cognitive, and mood disorders will be studied and related to neuropsychological measures of sustained attention, inhibitory control and impulsivity, and measures of cortisol and heart rate. If effects are found, they could broaden our knowledge of fetal programming and the origins of disorders in adolescence.

References


Rubia, K. (2002). The dynamic approach to neurodevelopmental psychiatric disorders: Use of fMRI combined with neuropsychology to elucidate the dynamics of psychiatric disorders, exemplified with and without ADHD. Behavioural Brain Research, 130, 47–56.


