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## High antenatal maternal anxiety is related to impulsivity during performance on cognitive tasks in 14- and 15-year-olds

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### Abstract

This study prospectively investigated the influence of antenatal maternal anxiety, measured with the State Trait Anxiety Inventory at 12–22, 23–31 and 32–40 postmenstrual weeks of pregnancy, on cognitive functioning in 57 adolescents (mean age 15 years). ANCOVAs showed effects of State anxiety at 12–22 weeks, after controlling for influences of State anxiety in later pregnancy and postnatal maternal Trait anxiety. Adolescents of high anxious pregnant women reacted impulsively in the Encoding task; they responded faster but made more errors than adolescents of low anxious women. They also scored lower on two administered WISC-R subtests. In the Stop task no differences in inhibiting ongoing responses were found between adolescents of high and low anxious pregnant women. We suspect that high maternal anxiety in the first half of pregnancy may negatively affect brain development of the fetus, reflected by impulsivity and lower WISC-R scores at 14–15 years. © 2004 Elsevier Ltd. All rights reserved.

**Keywords:** Pregnancy; Maternal anxiety; Fetal development; Inhibition; Follow-up; Impulsivity; Regulation problems

### 1. Introduction

Negative maternal emotional states during pregnancy have been shown to influence the development of the child to be born. The effects are observable prior to birth as well as in the neonate, infant and child (for a review, see [1–4]). High maternal anxiety and stress during pregnancy are for instance associated with alterations in fetal motor activity and heart rate patterns (e.g. [5–9]) and with childhood disorders such as attention deficit hyperactivity disorder (ADHD), externalizing and internalizing behavior [10–14]. ADHD symptoms (inattention, hyperactivity, impulsivity), externalizing behavior (aggression, acting-out behavior) and internalizing behavior (anxiety, emotional inhibition and lability) may be seen as problems with regulation at the cognitive level (e.g. attention problems, impulsive

cognitive style), behavioral level (e.g. hyperactivity) and emotional level (e.g. acting-out behavior, anxiety) (e.g. [15, 16]). In some studies the effects are only present when the negative maternal state occurs relatively early in the pregnancy. For instance, Van den Bergh and Marcoen [14] found an association between high anxiety at 12–22 weeks of pregnancy and ADHD symptoms, externalizing problems, and self-report anxiety in 8–9-year-old children, and did not find this association for high anxiety occurring later in gestation. In contrast, in the study of O'Connor et al. [11,12] the strongest effects were found for late gestation periods.

It is not known at present how maternal emotional states can induce these behavioral effects. Most likely, anxiety and stress related hormones originating from the mother play a crucial role. These hormones can enter the fetal organism [17], and if present during specific sensitive developmental periods, they are thought to disturb the programming of certain biological systems responsible for the regulation of fetal and later behavior [18–23]. For instance, a system well known from animal studies

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to be subject to such programming is the hypothalamic-pituitary-adrenocortical (HPA) axis [23], which is responsible for the regulation of homeostasis and reactions to stress [24, 25]. Antenatal maternal hormones could also disturb development of neuronal processes taking place during gestation. Subtle aberrations in neuronal proliferation, differentiation and migration processes taking place between 6 and 24 weeks of pregnancy, have been suggested to play a role in disorders such as ADHD, autism and some forms of schizophrenia (see [26–28]).

The present study represents the third wave of the prospective study of Van den Bergh and Marcoen [14] that investigates the influence of antenatal maternal anxiety on different aspects of neurobehavioral development and functioning of their firstborn children. As described above, the long term effects described in the literature by now are regulation problems at cognitive, behavioral and emotional level during childhood. Evidence for these regulation problems was based on mother and/or teacher report; some studies also rely on behavioral observations. The present study is the first one that examines effects of antenatal maternal anxiety into adolescence and the first one in which cognitive functioning (or cognitive regulation problems) is measured with standardized tasks. To this end, two computerized cognitive tasks and two subtests of the Wechsler Intelligence Scale for Children—Revised (WISC-R; [29,30]) were used.

Through clinical and neurophysiologic studies it is well established that regulation problems and the associated affected functions are critically mediated by the prefrontal cortex in syndromes such as frontal lobe lobectomy, visual neglect and schizophrenia [31–33] and in at least one subtype of children with ADHD ([34]; see [35] for a review). Consequently, the aim was to investigate the relationship between antenatal maternal anxiety and cognitive tasks, placing a load on prefrontal cortical functions. Three functions were chosen whose link with the prefrontal cortex is well established, namely visual attention control, working memory and response control [33,36–39] and these were measured with two cognitive tasks.

Visual attention control is required when subjects have to direct attention to a larger visual area or focus attention to a particular spatial location while ignoring information at other locations. Control of visual attention is mediated by a distributed functional network of areas in frontal and parietal lobes. The frontal areas involved are the medial prefrontal cortex (more specifically anterior cingulate gyrus) [33], and the cluster of areas generally referred to as the frontal eye fields [40,41]. Working memory load is manipulated by increasing the number of task related elements that have to be maintained at the same time in memory during performance. This function has been associated with the dorsolateral prefrontal cortex [42,43]. We evaluated visual attention control and working memory with the subtest *Encoding* of the Amsterdam Neuropsychological Tasks (ANT) [44].

Response control refers to the processes involved in the decision to actually perform a prepared response or to refrain from executing the response. In the present study, response control was assessed with the *Stop task paradigm* [45,46], which has been used to monitor the development of inhibitory control [47] and to measure response inhibition in children with disorders such as ADHD, conduct disorder, or anxiety disorders (for a review see [46]). Magnetic resonance imaging (MRI) and functional MRI (fMRI) studies of patients with ADHD have shown abnormalities in fronto-striatal circuitry during performance of stop tasks (e.g. [48,49]) and other kind or response inhibition tasks (e.g. [50]).

## 2. Subjects and methods

### 2.1. Participants

Of the 86 women and their firstborn children participating at the beginning of the study, 68 participated when the children were 14/15 years old. Of the latter, four adolescents did not participate in the cognitive tasks, data from one outlier were excluded, and data of six other participants could not be used due to computer failure. Consequently, data on 57 mother–child pairs were available for the present study. Twenty-nine of the participants were boys, 28 were girls. The mean age of the adolescents was 15 years (range = 14.54–15.54; SD = 3 months). The study was approved by the local ethical committee and all participants gave their informed consent.

At the start of the study all mothers were between the ages of 18 and 30 years, and nulliparous. They were between 12 and 22 weeks pregnant, and there were no obstetrical complications or medical risks. Although some of these women smoked during pregnancy ( $n=15$ ), none of them used other drugs or medication with risks for the fetus. Pregnancies were dated using the last menstrual period or, when dates were uncertain, with a sonographical examination. All participating mothers were Caucasian, Dutch-speaking and none of them had a psychiatric history.

All babies were born in the hospital between 36 and 41 weeks of gestation. Their mean birth weight was 3307 g (SD = 490.72). All babies scored high on Prechtl's list of 52 optimal obstetrical conditions ( $M=45.22$ ; SD = 2.7; [51]) and except for two babies, who had a score of 8, all of them had 5 min Apgar scores of 9 or 10.

### 2.2. Measures

#### 2.2.1. Maternal anxiety

Anxiety of the mother was measured three times during the antenatal part of the first wave of the study: during the period 12–22 weeks, 23–31 weeks and 32–40 weeks postmenstrual age. The Dutch version of the State Trait Anxiety Inventory (STAI; [52,53]) was used: this is a self-report questionnaire comprising two subscales of 20 items, scored from 1 to 4. Trait anxiety refers to a disposition or proneness to react with

anxiety, while State anxiety refers to a transient emotional state, characterized by subjectively experienced tension and an increased activity state of the autonomous nervous system. Chronbach's alphas are 0.95 and 0.93 for the state and trait anxiety scales, respectively [53]. The state anxiety subscale provides a valid measure of the intensity of transitory anxiety in response to real life stress [54]. Therefore, the three prenatal state (and not trait) anxiety measures—namely State anxiety at 12–22 weeks (State12–22), at 23–31 weeks (State23–31) and at 32–40 weeks (State32–40)—were included as predictors in our models investigating the effects of antenatal maternal anxiety.

Initially, three experimental anxiety groups were formed for each predictor: a low ( $<Pc25$ ), an average ( $\geq Pc25$  and  $<Pc75$ ) and a high ( $\geq Pc75$ ) anxiety group. Preliminary analyses of the scores obtained on the cognitive tasks revealed that for each predictor, the low and average anxiety groups did not differ significantly on any of the cognitive measures. Therefore analyses were carried out with only two anxiety groups for each predictor: a low–average ( $<Pc75$ ) and a high ( $\geq Pc75$ ) anxiety group.

The STAI was also postnatally completed by the mothers in each wave of the study: at 1, 10, and 28 weeks (postnatal part of first wave), at 8/9 years (second wave) and at 14/15 years (third wave). Because sustained high maternal anxiety in the course of childhood may affect the development of the child, we wanted to control for its possible influence on the dependent variables. To this end a principal component analysis was conducted on the five postnatal trait anxiety measures. This revealed one component, explaining 62% of the variance in all five measures. A variable consisting of the standardized component score for each mother was used as covariate in all analyses.

## 2.2.2. Cognitive tasks

### 2.2.2.1. Attention and working memory.

The first cognitive task, *Encoding*, is a subset of the Amsterdam Neuropsychological Tasks [44], intended to assess both visual attention and working memory. This task has been used to demonstrate attentional control and information processing deficits in children treated for leukemia [55] and phenylketonuria [56], and in patients with multiple sclerosis [57].

The stimuli appeared on a computer screen and participants had to respond by pressing a mouse-key using the thumb of both hands. 'Yes' and 'no' answers were assigned to the right and left mouse keys, respectively, for right-handed participants, and the other way around for left-handed participants. After a short explanation, memorization of the target(s) and practice runs, the actual task began. The participants had to attend to four letters appearing simultaneously on the screen. In part 1 of the task, one target letter had to be memorized (low memory load) and participants had to detect that one target letter in a set of four letters that were all either easy to encode (intact stimulus) or difficult to encode (degraded stimulus). If the target letter was present in the set of four, participants had to press the 'yes'-key (target present); if the target letter was absent they had to press the 'no'-key (target absent). In part 2, three letters had to be memorized (high memory load), and again the participants had to press 'yes' if one of the three target letters was present, and 'no' if none was present. Again the letters were all either intact or degraded. In both parts, participants were instructed to work as quickly and accurately as possible. The three conditions (present versus absent target; intact versus degraded stimulus; low versus high memory load) were administered 20 times, resulting in a total of 160 trials. Stimuli were shown until

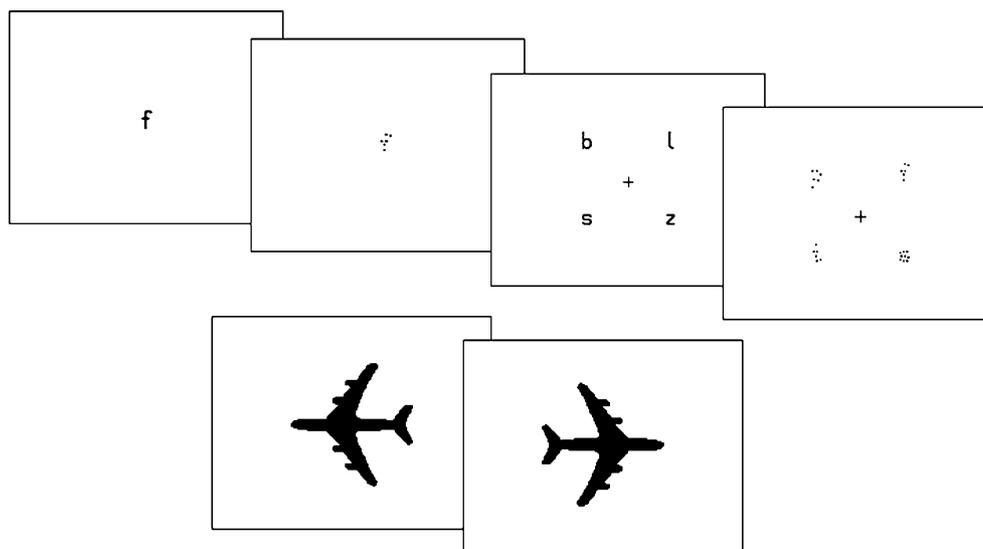


Fig. 1. Stimuli used in the Encoding task and Stop task. Above: stimuli used in the Encoding task, from left to right: intact target low memory load; degraded target low memory load; target absent intact low memory load; target present degraded low memory load. Below: airplane used in the Stop task.

the participant responded. The post-response interval was 1200 ms. Example stimuli are shown in Fig. 1.

The mean reaction time, the standard deviation of the reaction time for the correct answers and the percentage of correct answers given by a participant in the three conditions were used as performance measures. A visual attention control problem is revealed by a main effect of anxiety on one of the dependent variables. A working memory problem is revealed by an interaction of the group variable with the task variable memory load (low versus high memory load), when subjects in the high anxiety group have more difficulty when three letters have to be held in working memory. Of special interest are interactions between anxiety and target type (present versus absent present) and/or stimulus type (intact versus degraded stimulus) because these can qualify eventual deficits found. An interaction between anxiety and target type would indicate that adolescents of high anxious mothers have more problems when more information has to be processed. In a target present-trial, a target is present in the set of four letters, hence processing can be stopped when this target is found. In a target absent-trial on the other hand, no target is present, and this can only be concluded after investigating all four letters. An interaction between anxiety and stimulus type would signify differences between adolescents of low-average and high anxious mothers in the ability to encode the stimuli presented.

*2.2.2.2. Response control.* The *Stop task* was originally developed by Logan and Cowan [45] to measure response inhibition. The task was presented to the participants as a game in which they had to act as air-traffic controllers, safely landing airplanes by pressing a button. Two types of trials were used: go trials and stop trials. Go trials consisted of airplanes presented for a period of 1000 ms at the midpoint of the computer screen (see Fig. 1). Immediately before the go stimulus onset, a fixation point (500 ms in duration) appeared on the screen. If the airplane pointed to the right, participants were instructed to press the right response button. If the airplane pointed to the left, participants were instructed to press the left button. Subjects responded with their right hand index finger. The inter-trial-interval was 500 ms. Stop trials consisted of a go trial and a stop signal (a 1000 Hz tone, 50 ms in duration), presented through earphones. Adolescents were instructed not to press either of the two buttons when they heard the tone. Seventy-five percent of the trials were go trials, 25% were stop trials.

The Stop task commenced with two practice blocks. In the first only go trials were presented, in the second, 25% of the trials were stop trials. Participants were instructed to work as quickly and accurately as possible and to try to suppress their response when they heard the stop signal. After practice, participants were administered four experimental blocks of 64 trials. Within a block, the plane pointed equally often to the right as to the left, and stop signals were balanced for right

and left go trials. A stop trial was always followed by a go trial. However, to prevent children from expecting that a stop trial would always be followed by a go trial, in each block two stop trials were presented in succession.

The purpose of the Stop task is to estimate the speed of the inhibition process, or stop signal reaction time (SSRT). SSRT cannot be observed, because the response to a stop signal is a covert one. Therefore, SSRT has to be estimated. This can be done using the race model [45]. According to this model, the go process (leading to a button press) and the inhibition or stop process (leading to an inhibited response) are independent. On stop trials these two processes compete and the process that finishes first determines whether the response will be executed or not. To estimate SSRT, a tracking algorithm was used that varied the delay between the go stimulus and the stop signal [58–60]. The initial delay was 200 ms. If the participant inhibited his/her response correctly, the delay for the next stop signal was increased by 50 ms. If the participant failed to inhibit his/her response, the delay was decreased by 50 ms. By using this tracking mechanism, it was established that a participant had a 50% chance of response inhibition. This means that on average, the go and the stop process finished at the same time. In this way, the finishing time of the go process becomes an estimate of the finishing time of the stop process. SSRT could then be calculated by subtracting the mean delay from the mean go signal reaction time. For the stop task, SSRT was the primary performance measure. In addition, mean reaction time and standard deviation of reaction time were calculated from correct go trials, and the percentage of correct go trials was used.

*2.2.2.3. Intellectual abilities.* Two subtests of the Wechsler Intelligence Scale for Children—Revised (WISC-R; [29,30]) were administered. In the verbal subtest *Vocabulary* participants had to explain the meaning of single words. In *Block Design*, a visual construction task, the participants were required to rebuild geometrical red–white patterns using different, identical cubes, as fast as possible. Raw scores of both subtests were transformed to standardized scores, which were used as dependent variables in the analyses.

### 2.3. Data analysis

The relationship between maternal State anxiety at each of the three pregnancy periods and each of the measures of cognitive functioning was examined with analysis of covariance (ANCOVA). Scores for low-to-average and high anxiety groups were compared and in order to control for confounding effects of maternal anxiety during the two other periods of pregnancy and postnatal maternal trait anxiety, these three variables were included as covariates in all ANCOVAs performed. A significance level of 0.05 was used. The necessity to include these three variables as covariates, as well as other variables that might affect

developmental outcome and that were already controlled for in the second wave of our study (i.e. smoking during pregnancy, birth weight of the child, educational level of the parents; see [14]) was investigated in preliminary analyses (see Section 3).

### 3. Results

#### 3.1. Preliminary analyses: prenatal State anxiety measures and potential covariates

##### 3.1.1. Descriptives and correlational analyses for prenatal State anxiety measures

The mean State anxiety scores for the total group differed depending on the pregnancy period (see Table 1 for descriptive statistics). State12–22 was higher than State23–31 ( $t=3.9$ ,  $p<0.001$ ) and State32–40 ( $t=2.09$ ;  $p=0.042$ ). State23–31 and State32–40 did not differ ( $t=-1.47$ ;  $p=0.148$ ). As described above, subjects were classified

Table 1  
Descriptive statistics of State anxiety and correlations with potential covariates

	Prenatal State Anxiety		
	State12–22	State23–31	State32–40
<i>Descriptive statistics</i>			
<i>Total group</i>			
Mean	38.9	34.4	36.0
Standard deviation	8.5	8.9	7.6
Range	20–62	20–62	20–58
Percentile 75	43	39	40
<i>Low-average anxiety group</i>			
Mean	$n=41$	$n=40$	$n=40$
Standard deviation	34.5	30.0	32.5
Range	4.2	5.3	5.1
	24–41	20–38	20–39
<i>High anxiety group</i>			
Mean	$n=16$	$n=17$	$n=17$
Standard deviation	49.9	44.9	44.3
Range	6.4	6.7	5.7
	43–62	39–62	36–58
<i>Correlations</i>			
State anxiety 12–22 wks	$r^a$	–	0.36
	$p$		0.006
State anxiety 23–31 wks	$r^a$	–	0.33
	$p$		0.012
Postnatal trait anxiety	$r$	0.34	0.65
	$p$	<0.011	<0.01
Smoking frequency <sup>b</sup>	$r$	0.23	0.26
	$p$	ns	<0.05
Birth weight <sup>c</sup>	$r$	–0.11	–0.01
	$p$	ns	ns
Socio-economic status <sup>d</sup>	$r$	–0.14	–0.21
	$p$	ns	ns

Note  $n=57$ .

<sup>a</sup> Phi-coefficient on dichotomous variables.

<sup>b</sup> Number of cigarettes smoked daily during pregnancy.

<sup>c</sup> The child's birth weight adjusted for gestational age at birth.

<sup>d</sup> The socio-economic status of the parents was inferred from both parents' educational level, coded on a 4-point scale ranging from primary education only to having a university degree.

into a high and a low-to-average maternal anxiety group for each pregnancy period, with Pc75 as cut-off score. The values of Pc75 are similar (for State12–22) or slightly lower (for State23–31 and State32–40) than the value of Pc75 in a reference population. The mean values of State anxiety in the high anxious group are situated at Decile 8 (for State12–22) and Decile 7 (for State23–31 and State32–40) of that reference population (i.e. the non-clinical female Dutch community sample described in the STAI manual [53]). Decile 7 includes State anxiety scores ranging from 41 to 45, Decile 8 includes scores from 46 to 49). These data indicate that for the State anxiety measure, a substantial proportion of the women scored in the higher range. To see the extent of the dependency of the classification of the participants in the three periods, intercorrelations were calculated. As can be seen in Table 1, the correlations were significant. Therefore it was decided to include the measures of maternal State anxiety in the two other periods as covariates in the analysis for each maternal State anxiety measure.

##### 3.1.2. Correlational analyses of potential covariates

Table 1 also presents correlations of three State anxiety measures with postnatal maternal trait anxiety and with three other variables that might affect developmental outcome and that were controlled for in the second wave of our study. Including all significantly correlated variables was not possible because of the small sample size. It was decided to include also postnatal Trait anxiety in all ANCOVAs since this was the only variable that was significantly correlated with all three prenatal State anxiety measures.

#### 3.2. Encoding task

The relationship between each prenatal maternal State anxiety measure and each dependent variable of the Encoding task (mean reaction time (MRT), the standard deviation of the reaction time for the correct answers, and the percentage of correct answers) was analyzed with repeated measures ANCOVAs, with anxiety as between-subjects variable and the task variables (target type, stimulus quality, memory load) as within-subject variables. As indicated, in ANCOVAs of one of the three State anxiety measures the two other State anxiety measures as well as postnatal Trait anxiety were entered as covariates. These analyses revealed a significant main effect of State12–22 on MRT ( $F(1,52)=6.01$ ;  $p=0.018$ ), an interaction effect of State12–22 with target type for the percentage of correct answers ( $F(1,52)=4.09$ ;  $p=0.048$ ), as well as a main effect of State12–22 for the latter ( $F(1,52)=5.91$ ;  $p=0.019$ ). State23–31 and State32–40 did not significantly affect any of the dependent variables.

The main effect of State12–22 on MRT indicated that adolescents of high anxious mothers responded overall faster than adolescents of low-average anxious mothers.

None of the task variables interacted significantly with State12–22 (largest  $F$  value was for the interaction with memory load:  $F(1, 52)=2.98, p=0.09$ ). There was also no significant effect of any of the covariates. The reaction time results are graphically presented in Fig. 2.

The interaction effect of anxiety with target type on the percentage of correct answers indicated that, next to being faster, adolescents in the high anxiety group also made more errors in trials where no target was present and all four letters had to be processed to establish the correct answer. This was confirmed in post hoc analyses (Tukey Test): target present trials  $p=0.867$ ; target absent-trials  $p=0.019$ ). As can be seen in Fig. 3, the percentage of correct answers of the high anxiety group was lower than in the low-average anxiety group in the Target absent (TA) conditions. There was no significant effect of any of the covariates.

3.3. Stop task

One-way ANCOVAs were conducted to investigate the effect of each prenatal maternal State anxiety measure on each of the performance measures of the Stop task (stop signal reaction time (SSRT; estimated speed of inhibition), mean go trial reaction time (MRT), standard deviation of go trial reaction time (SDRT), and percent correct responses in go trials). Again, the two other State anxiety measures and the postnatal Trait anxiety score were entered as covariates. None of these analyses revealed a statistically significant effect of prenatal anxiety.

For all dependent variables the highest  $F$ -values were observed for State12–22 anxiety, with  $F(1,52)=1.31$  ( $p=0.257$ ) for SSRT,  $F(1,52)=2.40$  ( $p=0.127$ ) for MRT,  $F(1,52)=3.66$  ( $p=0.061$ ) for SDRT, and  $F(1,52)=1.09$  ( $p=0.302$ ) for percent correct responses in go trials. So, there was only a borderline significant effect observed, in that subjects in the high State12–22 anxiety group showed more variability in their reaction time in the go-trials. There was no difference in the estimated speed of the inhibition

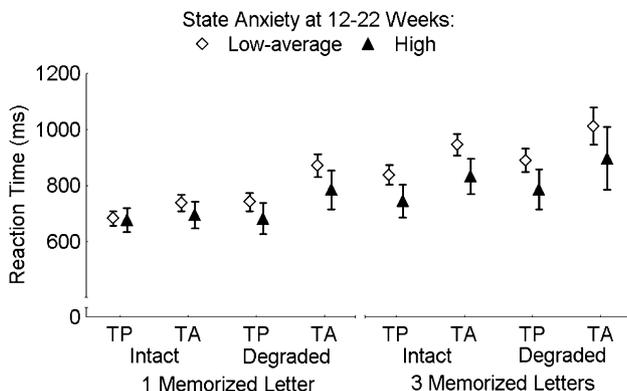


Fig. 2. Mean reaction time  $\pm$  standard deviation in the different conditions of the Encoding task for the adolescents of mothers with low-average and high levels of anxiety during 12–22 weeks of pregnancy. TP, target present; TA, target absent.

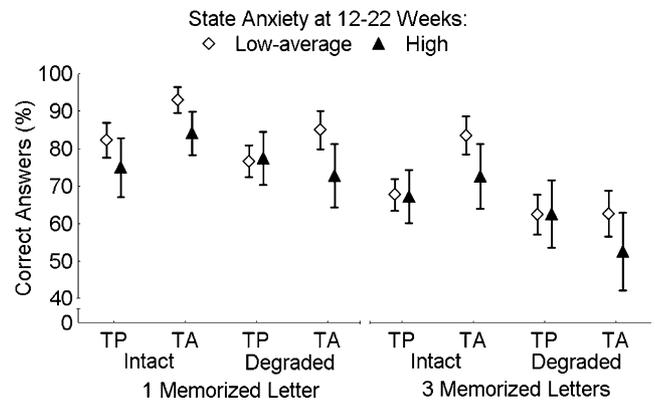


Fig. 3. Percentage of correct answers  $\pm$  standard deviation in the different conditions of the Encoding task for the adolescents of mothers with low-average and high levels of anxiety during 12–22 weeks of pregnancy. TP, target present; TA, target absent.

process (SSRT). It should be noted that both groups reached an equal level of response inhibition around 50% as predicted by the tracking algorithm (this proves that the algorithm worked properly).

3.4. Vocabulary and Block Design

The effect of the three prenatal maternal State anxiety measures on the two WISC-R subtests Vocabulary and Block Design was analyzed with a repeated measures ANCOVA with prenatal anxiety as between-subjects variable and the standardized scores on the two subtests as within-subjects repeated measures variable. The other two State anxiety measures and the postnatal anxiety score were again used as covariates and again did not reach significance. However, the analyses yielded a significant effect of State12–22 on subtest performance ( $F(1,52)=7.13, p=0.010$ ). There was no significant result for State23–31, nor for State32–40 ( $F=1.55$  and  $F=0.58$ , respectively). Planned comparisons for the effect of State12–22 on each of the subtests separately showed that adolescents in the high State12–22 anxiety group obtained lower scores on the subtest Vocabulary ( $F(1,52)=5.85, p=0.019$ ). A similar trend was observed for the scores on the Block Design subtest, but the effect was only of marginal significance ( $F(1,52)=3.40, p=0.0708$ ). Mean standard scores and standard deviations for both Vocabulary and Block Design are shown in Table 2.

Table 2  
Descriptives for the WISC-R subtests

Intelligence subtests		Low-average anxiety group	High anxiety group
Vocabulary	Mean	13.71	11.44
	SD	2.62	2.73
Block Design	Mean	12.18	10.16
	SD	2.83	3.19

Vocabulary and Block Design are intended to assess global cognitive ability. The IQ estimated from these two subtests combined correlates  $r=0.90$  with the Full Scale WISC-R IQ [61]). The significant effects of antenatal maternal anxiety on the performance in the encoding tasks and the WISC-R subtests raise the question whether the specific problems observed in the Encoding task in adolescents of high anxious mothers merely reflect a lower general cognitive ability level or whether they are specific attentional or cognitive control problems not reducible to intelligence. To test this hypothesis the analyses of the effects of State12–22 on the reaction time and the percentage of correct answers on the Encoding task were re-computed with the scores on the two WISC-R subtests as additional covariates. For the reaction time this again yielded a significant main effect of anxiety ( $F(1,50)=4.44$ ,  $p=0.040$ ). For the percentage of correct answers the effect of the prenatal anxiety level no longer reached significance ( $F(1,50)=2.25$ ,  $p=0.140$ ), nor did the interaction with the target type of the trials ( $F(1,50)=1.26$ ,  $p=0.268$ ). However, although weakened, the post hoc contrast analysis with the Tukey Test indicated that the same pattern of making more errors (i.e. only in the target absent-trials) was still evident. Whereas there was no difference in target present trials ( $p=0.807$ ), subjects from the high anxiety group made more errors on target absent trials ( $p=0.005$ ).

### 3.5. The effect of gender

As reported by Van den Bergh and Marcoen [14], mothers carrying a boy had marginally significant higher State12–22 scores than mothers carrying a girl. Hence, it is of interest to investigate whether there is a differential effect of antenatal maternal anxiety on boys and girls. Therefore, exploratory analyses were performed for the reaction time and the percentage of correct answers on the Encoding Task, with gender as second between-subjects variable (next to State anxiety). Results are shown in Fig. 4. For the mean reaction time, no significant anxiety by gender interaction was observed. However, for the percentage of correct

answers the anxiety by gender interaction was significant ( $F(1,50)=5.94$ ;  $p=0.018$ ). Boys in the high anxiety group committed more errors than boys in the low-average anxiety group. This difference was not evident in girls. As similar to the previous analysis without gender as between-subjects variable, post hoc tests (Tukey tests) showed that boys in the high anxious group committed more errors in target absent-trials ( $p=0.01$ ). The anxiety by gender by target present versus target absent interaction was however not significant.

For the intelligence subtests, the anxiety by gender interaction was not significant ( $F(1,50)=2.36$ ,  $p=0.13$ ). However, analyses using pooled data for both intelligence subtests, showed that boys in the high anxiety group tended to obtain lower scores on both intelligence subtests than boys in the low-average anxiety group (Fig. 5). This trend was not evident in girls. The anxiety by gender interaction probably did not reach significance due to small amount of girls (only five) in the high anxiety group and the relatively large standard deviation.

## 4. Discussion

This study prospectively investigated the influence of maternal State anxiety measured at 12–22, 23–31 and 32–40 weeks of pregnancy, on cognitive functioning in adolescents. ANCOVAs showed an effect of anxiety at 12–22 weeks only. Adolescents of mothers who were highly anxious during the 12–22nd week of pregnancy responded faster in the Encoding task and made more errors in the target present condition of that task, indicating an impulsive response pattern. They also scored significantly lower on two intelligence subtests. Both results are particularly strong since they were found after controlling for maternal state anxiety at both later pregnancy periods and for postnatal maternal trait anxiety. Most of the results on the Encoding task remained significant after controlling for the performance on the two intelligence subtests. However, in the Stop task the speed and accuracy of the inhibition response

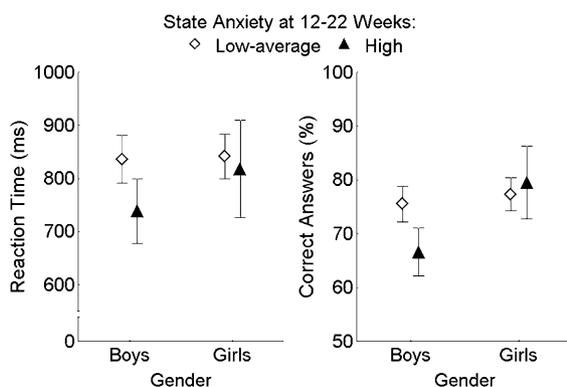


Fig. 4. State 12–22 by gender interaction for the mean reaction time (left) and the percentage of correct answers (right).

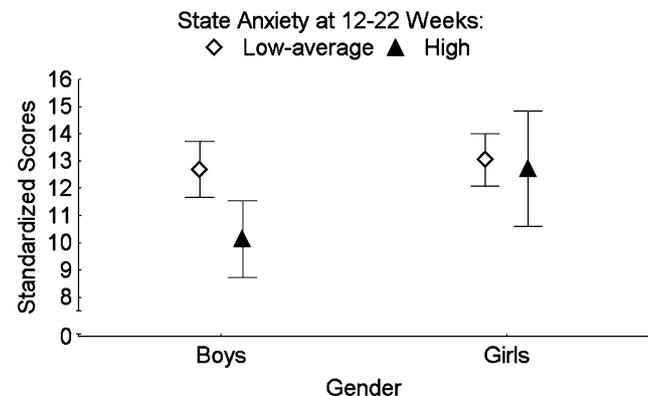


Fig. 5. Anxiety by gender interaction for the pooled data of both intelligence subtests.

turned out to be unaffected in adolescents of highly anxious mothers. Earlier findings showed that children of mothers with high anxiety during pregnancy showed more problems with regulation at the cognitive, behavioral, and emotional level [10–14]. In this study we specifically examined regulation problems at the cognitive level as outcome measure; in general our findings are in line with earlier findings.

*First*, the adolescents from the high anxiety group reacted significantly faster than adolescents from the low–average anxiety group. There was no interaction with any of the task conditions, indicating that responding fast was a general response characteristic not influenced by task variables (present versus absent target, intact versus degraded stimulus, low versus high memory load). It is for instance possible that these adolescents had a shorter mean reaction time because they did not investigate all letters. If this were so, this pattern would be more apparent when no target was present and hence all four letters had to be processed, than when one of the four presented letters was a target and processing could be stopped as soon as this target was found. This was not confirmed by the data, however, since there was no interaction between state 12–22 anxiety and target type for reaction time. In addition to responding faster, adolescents of mothers who reported high State anxiety during 12–22 weeks of pregnancy made more errors than adolescents in the low–average anxiety group; a significant anxiety by target type interaction revealed that this pattern was only apparent in the target absent trial where all four letters have to be processed before an adequate response can be given. Taken together, reacting faster but making more mistakes can be labeled as impulsive. Our results indicate that the effect of prenatal anxiety on this impulsive response pattern did not disappear when controlling for the performance on the two intelligence subtests, indicating that it is a specific cognitive regulation problem or impairment.

*Second*, another significant finding was that adolescents of mothers with high anxiety at 12–22 weeks of pregnancy had lower scores on Vocabulary and Block Design, two subtests of the WISC-R. Given that the IQ estimated from these two subtests correlates  $r=0.90$  with the Full Scale IQ [19], this result suggests that adolescents of mothers who were highly anxious at 12–22 weeks of pregnancy have lower intellectual abilities than adolescents of low-to-average anxious mothers. Or the other way around, the reduced scores on these subtests may have resulted as a secondary effect of these adolescents' tendency for impulsive responding. At least for the subtest Block Design, observations during performance of the task suggest that impulsivity was part of the reason why the adolescents obtained lower scores. Adolescents in the high anxiety group tended to rapidly (impulsively) construct a pattern, then noticed that they made an error and had to rebuild it, eventually taking more time than an adolescent in the low–average anxiety group who immediately constructs

the correct pattern. It is clear that more extensive research is needed in which complete intelligence scales are administered before conclusions can be drawn regarding the effect of antenatal maternal anxiety on intellectual development. In contrast to the positive results found in the Encoding task and intelligence subtests for maternal anxiety at 12–22 weeks of pregnancy, analyses of the performance on the Stop task revealed no significant results. Most importantly, there was no difference between adolescents of the high versus low–average anxiety group in the duration and accuracy of the inhibition process as estimated from performances in the stop trials of that task.

The results of the present study indicate that maternal State anxiety during pregnancy has long term associations with the cognitive development of the child to be born. These associations emerged as increased impulsivity in responding in the target(s) absent conditions of the Encoding task, and as lower scores on two intelligence subtests. The specific cognitive regulation problem expressed in the performance on the Encoding task seems not to be related to a working memory problem (because anxiety did not interact with memory load) nor to the speed of the visual attention processes when scanning the stimuli (since a main effect indicated a shorter mean reaction time in the high anxiety group). However, a plausible explanation for the observed problem was found when looking at differences in the characteristics of the non-target trials of the Encoding task (where impulsivity was observed) and the stop trials of the Stop task (where an adequate response inhibition was achieved). The most obvious difference between these two conditions is that in the stop trials of the Stop task an external signal is provided: a sound presented through earphones warns the child when it has to withhold from pressing the left or right key. The stop signal may exogenously trigger response control processes and facilitate the inhibition process due. In the non-target trials of the Encoding task no external signals are available that can trigger response control processes but instead these processes have to be generated endogenously (i.e. from within the subject). We observed that under these conditions, adolescents in the high anxiety group have more difficulties in withholding the 'yes'-response long enough in order to be able to give the correct answer (in this case a 'no'-response) than adolescents from the low–average anxiety group. So, the cognitive regulation problem of adolescents of mothers who were highly anxious at 12–22 weeks of pregnancy seems to be related to problems with endogenous response control processes and is, for instance, expressed when they have to continue the inhibition of a response for a longer time without external signals encouraging the inhibition.

The distinction between endogenous and exogenous response control processes receives support from the fact that several functions involving the prefrontal cortex, such as vigilance (or the ability to sustain an alert state) [26], the directing of attention [62], and generating simple and

complex motor patterns [63,64] have been shown to involve different areas depending upon whether they were externally triggered or internally generated.

An important question with regard to fetal programming is the time period of pregnancy during which the fetus is most vulnerable to maternal hormonal influences. Previous results of our follow-up study showed that maternal State anxiety at 12–22 weeks of pregnancy was associated with ADHD symptoms, externalizing problems, and self-report anxiety at 8/9 years of age [14] as well as with increased motor activity at 36–38 weeks postmenstrual age and during the first 7 months of life [8,65]. The present results show that effects of maternal anxiety on cognitive development are only observable when anxiety is experienced at 12–22 weeks, and not thereafter. Whether the vulnerability starts before week 12 or is confined to a specific moment within this 10 week period, is yet unknown. In humans, the period from 8 to 24 weeks postmenstrual age is especially important because the proliferation, differentiation, and migration of neurons take place and because several brain areas (e.g., hippocampus, amygdala, anterior cingulate cortex, brainstem) functionally connected to the prefrontal cortex [66] are already differentiated during that period. The prefrontal cortex differentiates relatively late and its basic six layered cytoarchitectonic pattern is established only at 26–34 weeks of gestation [67,68]. Although the PFC has been shown to be involved in most forms of complex self-regulation [36,69], it is important to note that the PFC is just a relay-station in many complex neural systems on which behaviour ultimately relies. It plans specific actions and then orders more posterior and subcortical areas of the brain to execute these actions while coordinating and implementing feedback of the different executive and sensory systems [37,70]. Therefore, it is likely that a dysfunction of the PFC, as seen in our study, can be associated with a dysfunction in one or more of the related systems. It is plausible that the hormonal factors related to maternal State anxiety at 12–22 weeks interfered with some of the complex neuro-developmental processes taking place at that gestation period.

#### 4.1. Strengths and limitations

A first, obvious strength of our study is the prospective design with a retention rate of 66–79% over a period of about 15 years. Second, maternal anxiety was measured repeatedly during gestational periods that are assumed to be critical windows for brain development and also at different postnatal periods. The whole range of anxiety in a normal, non-clinical population was covered in our sample and a substantial part of the women scored in the higher range. *Third*, standardized measures of cognitive functioning (computerized cognitive tasks and intelligence subtests of the WISC-R) were used.

Some limitations of the study must be mentioned. First, the sample was rather small and results might be sample

specific. Second, only a limited selection of instruments was used for the assessment of cognitive functioning. It is clear that conclusive evidence from other tasks tapping prefrontal functioning and making a distinction between exogenously and endogenously triggered response control processes are needed before firm conclusions can be reached. Third, although some anxiety by gender interactions and some post hoc comparisons were statistically significant, it should be borne in mind, that there were only five girls compared to eleven boys in the high anxiety group. Therefore, further research is needed to clarify whether there is a differential impact of antenatal maternal anxiety on boys and girls.

#### 4.2. Clinical implications

Only few studies have investigated mother-fetus interactions and the consequences these interactions have for the postnatal life of the child with standardized behavioural observations. We were able to relate the mother's anxiety level during the 12–22nd week of pregnancy to observed difficulties in performances on a computerized cognitive task and intelligence subtests. More studies are needed to understand the nature of these effects. However, our results underline the need for early prevention and intervention programs for highly anxious women. Preferentially, prevention and intervention should even be achieved before pregnancy starts.

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