Developmental brain alterations in 17 year old boys are related to antenatal maternal anxiety

Mennes, M.; Van den Bergh, B.R.H.; Lagae, L.; Stiers, P.

Published in:
Clinical Neurophysiology

Publication date:
2009

Document Version
Publisher's PDF, also known as Version of record

Clinical Neurophysiology xxx (2009) xxx–xxx

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Developmental brain alterations in 17 year old boys are related to antenatal maternal anxiety

Maarten Mennes [a,c,*,1], Bea Van den Bergh [b,c], Lieven Lagae [a], Peter Stiers [a,d]

[a] Department of Woman & Child, Section Paediatric Neurology, K.U.Leuven, Leuven, Belgium
[b] Department of Psychology, Tilburg University, Tilburg, The Netherlands
[c] Department of Psychology, K.U.Leuven, Leuven, Belgium
[d] Department of Neuropsychology and Psychopharmacology, Maastricht University, Maastricht, The Netherlands

ARTICLE INFO

Article history:
Accepted 7 April 2009
Available online xxxx

Keywords:
Pregnancy
Environmental
P2
Adolescents
ERP

ABSTRACT

Objective: To assess the association between maternal anxiety during pregnancy and the brain activity of 17 year old adolescents performing two cognitive control tasks.
Methods: Twenty-three 17 year old boys of mothers whose level of anxiety was measured during pregnancy were investigated using ERP while performing a Go/Nogo paradigm assessing exogenous cognitive control and a Gambling paradigm requiring endogenous cognitive control.
Results: No effects of antenatal maternal anxiety were observed in the Go/Nogo paradigm. However, in the Gambling paradigm adolescents of the high anxiety group ($n = 8$) showed a less efficient pattern of decision making compared to the adolescents in the low-average anxiety group ($n = 15$). Moreover, only for this task the ERP data showed an enlarged early frontal P2a component in the high anxiety group.
Conclusions: The brain activity of adolescents during an endogenous cognitive control task is associated to the level of anxiety experienced by their mother during pregnancy. This association was not observed during an exogenous cognitive control task.
Significance: This study indicates that a child's brain functionality is related to its mother's anxiety during pregnancy. Endogenous cognitive control is regarded the cognitive function most affected by the level of antenatal maternal anxiety.

1. Introduction

Accumulating evidence indicates that the cognitive development of a child is related to the level of anxiety or stress experienced by its mother during pregnancy (e.g., Brouwers et al., 2001; Laplante et al., 2004; Bergman et al., 2007). However, most studies used the Bailey Scales of Infant Development or school results to assess cognitive abilities. As such research on the effects of antenatal maternal anxiety on specific cognitive functions is scarce. In a prospective longitudinal study our group showed that 15 and 17 year old adolescents born to mothers reporting high levels of state anxiety during weeks 12–22 of their pregnancy had long-term impairments in endogenous control of their performance on challenging cognitive tasks (Van den Bergh et al., 2005, 2006; Mennes et al., 2006). Endogenous cognitive control refers to the ability to generate triggers from within oneself or endogenously in order to control actions, strategies and thoughts interfering with optimal task performance (Miller, 2000; Miller and Cohen, 2001; Brass and von Cramon, 2004). It is opposed to exogenous cognitive control where cognitive control is triggered by external signals (e.g., a sound). Other cognitive functions associated with prefrontal functioning, such as working memory and attentional orienting, were not related to antenatal maternal anxiety (Van den Bergh et al., 2005; Mennes et al., 2006; Gutteling et al., 2006).

Based on these results orbitofrontal cortex was hypothesized as the area of the brain most influenced by antenatal maternal anxiety (Mennes et al., 2006). However, although inferences about the underlying brain functionality can be made based on the behavioral neurocognitive measures used in our previous studies, we did not measure actual brain functioning. Therefore, the purpose of the present study was to strengthen our previous finding of an impairment in endogenous control in adolescents of mothers reporting high levels of anxiety during the first weeks of pregnancy by monitoring the adolescents' electrical brain activity with event-related potentials (ERP).

* Corresponding author. Address: Section Child, UZ Gasthuisberg O&N1 Bus 504, Herestraat 49, 3000 Leuven, Belgium. Tel.: +32 16 33 00 21.
E-mail address: maarten.mennes@nyumc.org (M. Mennes).
[1] Present address: Phyllis Green and Randolph Cowen Institute for Pediatric Neuroscience, NYU Child Study Center, 215 Lexington Ave., 14th Floor, New York, NY 10016, USA.

1388-2457/$36.00 © 2009 International Federation of Clinical Neurophysiology. Published by Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.clinph.2009.04.003

Physiological measures, such as ERPs, are more closely related to underlying biological processes compared to complex behavioral measures. The use of physiological measures can provide an important impetus for research into the mechanisms of the relationship between antenatal maternal anxiety and later development. In primates for instance, dopamine receptors, that are also linked to the development of ADHD (Durston and Konrad, 2007), were found to be influenced by the level of antenatal maternal anxiety (Schneider et al., 2008). Although some studies on antenatal maternal anxiety in humans have investigated physiology by looking at the relationship between antenatal anxiety and hormones such as cortisol (O'Connor et al., 2005; Van den Bergh et al., 2008), evidence on actual brain functioning is lacking.

Here, in light of our previous results, we contrasted ERPs measured during an exogenous control task to those measured in an endogenous control task. Exogenous control is commonly assessed with tasks such as the Stop-task or Go/Nogo (Rubia et al., 2001; Nieuwenhuis et al., 2003; Liotti et al., 2007; Nigg et al., 2008). In the Stop-task an external stimulus should trigger response inhibition, and in a Go/Nogo task, which we used here, the stimuli clearly indicate which response should be given. Endogenous cognitive control on the other hand, can be assessed using different paradigms. For instance task-switching and dual task paradigms are often used (Gehring et al., 2003; Wylie et al., 2003). Here we assessed endogenous control using a newly developed gambling paradigm (Mennes et al., 2008).

2. Methods

2.1. Subjects

Twenty-three boys were included in the current study. They were a subgroup of the adolescents of our longitudinal study that participated in the behavioral cognitive assessment at age 17 ($n = 49$; Mennes et al., 2006). Only boys were included since our previous results yielded more consistent results in boys. This might be due to the fact that the assessed cognitive functions are more likely to be associated with antenatal maternal anxiety in boys, compared to a higher chance for mood-related disorders in girls (Van den Bergh et al., 2008).

Maternal anxiety was measured during pregnancy using the State-Trait Anxiety Inventory (Van der Ploeg et al., 1980). State anxiety was used as this subscale provides a measure of the intensity of transitory anxiety in response to real life stress. A cut-off score of 43 delineated a low-average and high anxiety group (cf. Mennes et al., 2006). Only anxiety measured during weeks 12–22 of pregnancy was used as our previous results on adolescent cognitive functioning showed effects of this period only (Van den Bergh et al., 2005, 2006; Mennes et al., 2006). Eight boys were included in the high anxiety group, 15 in the low-average anxiety group. The high anxiety group included almost all adolescents whose mother's anxiety score exceeded the cut-off score of 43. The adolescents comprising the low-average anxiety group were included based on availability. All subjects were 17 years old and born between 36 and 41 weeks of gestation with a mean birth weight of 3419 g (SD = 640 g) and 5 min Apgar scores of 9 or 10. The local ethical committee for experiments on human subjects approved the study. All subjects gave written informed consent.

2.2. Paradigms

Exogenous response inhibition was assessed with a classical *Go/Nogo* paradigm. Subjects were required to press a button with their dominant thumb as quick as possible whenever a square appeared in the middle of a computer screen (Go), however they should inhibit this response whenever a circle appeared (Nogo). Go trials had a probability of .80 vs. .20 for the Nogo trials. All subjects completed one run of 120 trials.

The results of the Go/Nogo paradigm were contrasted with those of a *Gambling* paradigm (for a complete description see Mennes et al., 2008). Subjects engaged in a computer gambling game and were verbally motivated to earn as many points as possible. Each trial consisted of a horizontal bar divided in two colored parts, each side indicating the probability of an imaginary token being hidden underneath (e.g., 30% blue–70% yellow). The size of each colored part in relation to the total bar could range from 5%–95% to 50%–50%. Subjects could guess the side they thought the token was hidden by pressing the corresponding response button. Points could be won or lost depending on the correctness of the subjects' guess. The amount of points that could be won was indicated above the bar (range 10–100). The points that could be lost were shown below the bar (range 0–100). An important feature of the task was that subjects were allowed to opt out of gambling (i.e. to pass) whenever they felt insecure about the trial. All they had to do was withhold the key-press response and wait until the stimulus disappeared. Passing was always rewarded 20 points. After each trial the result of that trial and the total score were shown. All subjects received 100 points as initial credit. After one practice run (20 trials) all subjects completed three runs of 50 trials. Four trial groups could be dissociated depending on the characteristics of the gambling stimulus: GO, NOGO, GAMBLE, and PASS (Mennes et al., 2008). However, these trial conditions were of no interest for the current study.

2.3. Electroencephalogram recording

EEG was recorded from 19 Ag/AgCl electrodes at 1000 Hz (bandpass = 0.095–70 Hz). Fp1, Fp2, F3, F4, F7, F8, C3, C4, T3, T4, P3, P4, T5, T6, O1, O2, Fz, Cz and Pz were placed according to the international 10–20 system with a ground electrode above the nose. Two electrodes were placed on the outer canthi and two above and below the right eye to detect horizontal and vertical eye movements. All electrodes were referenced to linked mastoids and impedances were kept below 5 kΩ. Offline analysis of the data, including a 30 Hz low-pass filter and removal of eye movement artifacts (using independent component analysis (Jung et al., 2000)), was performed using the EEGLAB v4.515 toolbox (Delorme and Makeig, 2004) under Matlab v7.0 (Mathworks, Natick, MA).

2.4. Data analysis

The behavioral data were analysed using repeated measures ANCOVA. Anxiety was used as between subjects factor (low-average vs. high). For Go/Nogo, Condition (Go vs. Nogo) was used as within subjects factor. For Gambling two within subject factors were specified: Action (gamble vs. inhibition responses) and Trial-type (determined vs. underdetermined). To control for the possible effects of anxiety during the other periods of pregnancy and during postnatal development, maternal state anxiety during weeks 23–31 and 32–40 of pregnancy, and a composite score of maternal trait anxiety measured at all postnatal follow-up stages were entered as covariates into the analysis. All behavioral data were log-transformed to improve normal distribution.

The primary analysis of the ERP data was done using a novel technique based on statistical parametrical mapping (SPM), which is widely used in fMRI research. The benefit of this procedure compared to traditional statistics used in ERP analysis is that it allows for a simultaneous statistical comparison across all time points included in the EEG epochs and across all channels included in the EEG recording. This avoids the subjective selection of time points and electrodes for statistical analysis. In-

Please cite this article in press as: Mennes M et al. Developmental brain alterations in 17 year old boys are related to antenatal maternal anxiety. Clin Neurophysiol (2009), doi:10.1016/j.clinph.2009.04.003

stead, the SPM analysis objectively indicates *where* and *when* significant effects occur. SPM is a mass univariate approach in which spatiotemporal neuroimaging data are modeled within the statistical framework of the general linear model. EEG epochs were entered into the analysis as space–time volumes with the anterior–posterior and left–right dimensions of each electrode's position as a 2-dimensional spatial array. Time was entered as a third dimension. As such voxels were defined containing the amplitude information at 1 electrode (with X and Y dimension), at 1 ms.

In a first level analysis beta maps for each subject in each condition were calculated by running a fixed effects analysis on each task condition for each subject. These beta maps were used in a second level random effects ANOVA to calculate condition related effects. For Go/Nogo an Anxiety (low-average vs. high) × Condition (Go vs. Nogo) analysis was done. For Gambling an Anxiety × Action (gamble vs. inhibition response) × Trial-type (determined vs. underdetermined) analysis was used. The effect of anxiety was tested in a one-sided (low-average < high) comparison. The threshold for significance was set at .001 uncorrected for multiple comparisons. We used the SPM5 package (Wellcome Department of Cognitive Neurology, University College, London, UK). Further exploration of peak-to-peak ERP values and confirmation of the results obtained with SPM was done using ANCOVA with repeated measures where necessary. A significance level of .05 was used.

3. Results

3.1. Behavioral results

3.1.1. Go/Nogo

There was no effect of the level of antenatal maternal anxiety on the mean reaction time, the standard deviation of the reaction time, or the number of correct responses measured in this task.

3.1.2. Gambling

The level of anxiety measured during pregnancy was associated with the distribution of gamble/inhibition responses across trials (Fig. 1). This distribution was quantified in a contrast measure defined as $(M - S)/(S + M)$ where S is the proportion of gambles in trials with a gain ⩽ the reward for an inhibition (i.e. 20 points) and M the proportion of gambles in all other trials. This contrast ranges between −1 (only gambles in the first kind of trials) and 1 (only gambles in the other trials), with 0 indicating equal percentages of gambles in both trial categories. The contrast for the adolescents in the low-average anxiety group (Mean = 0.93, SD = 0.04) was higher compared to the contrast for the high anxiety group (Mean = 0.75, SD = 0.14) ($F(1, 18) = 31.75$; $p < .001$), indicating that the adolescents in the high anxiety group gambled more in trials where others inhibited and less where others chose to gamble. As is evident from the scatterplot in Fig. 1 this effect could not be attributed to outliers.

In addition, there was a trend towards lower total scores achieved by the high anxiety group ($F(1, 18) = 4.08$, p = ns; Mean low-average = 4544 points, SD = 1035.28 vs. Mean high = 3642.5 points, SD = 1848.82). There was no effect of anxiety on the reaction time and the standard deviation of the reaction time.

3.2. ERP results

3.2.1. Go/Nogo

The level of anxiety was not associated with the ERPs measured in the Go and Nogo trials. The low-average < high anxiety SPM contrast for both trial conditions yielded no significant results, as is evident from Fig. 2 by the equal ERP waveforms for both anxiety groups in the Go and Nogo condition.

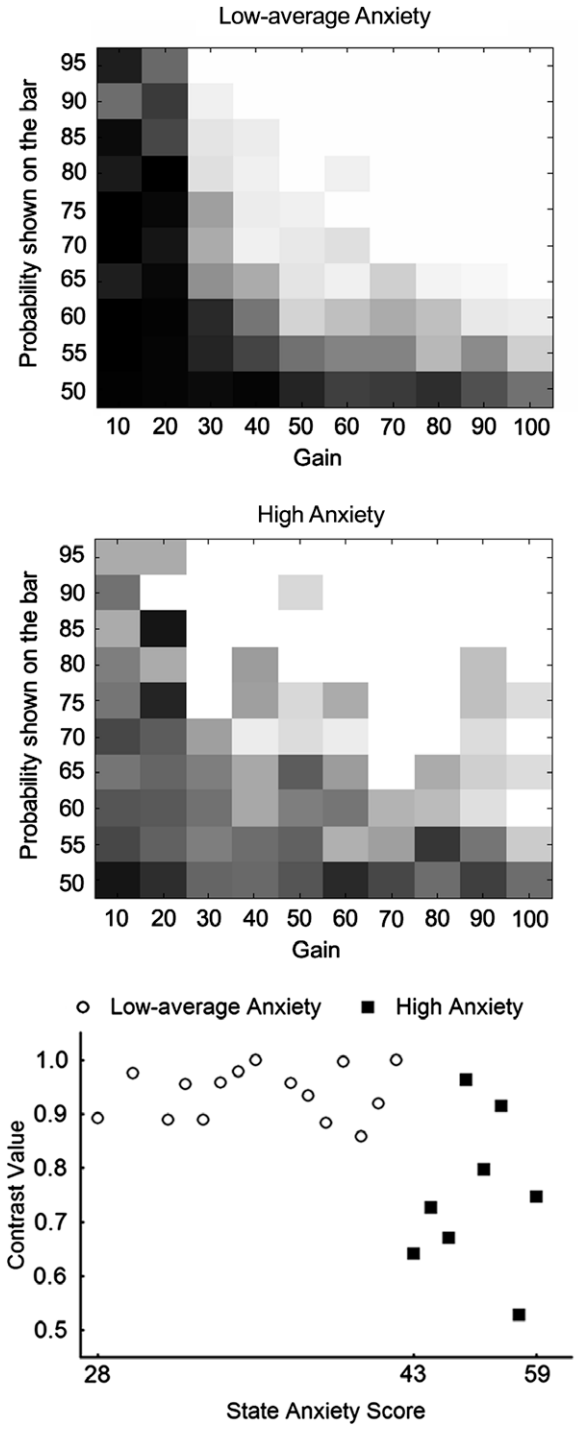

Fig. 1. Percentage of gambles made in the different trials of the Gambling paradigm for the low-average and high anxiety group. Each square represents the percentage of gambles made in a specific trial. Trials are ordered according to the proportional division of the stimulus bar (Y-axis) and the amount of points that could be won (X-axis). As such, the upper right square represents the percentage of gambles made in a trial where 100 points could be won and the proportional division of the bar was 95–5%. The lower left square represents the percentage of gambles made in a trial where 10 points could be won and the proportional division of the bar was 50–50%. Lighter squares indicate a higher percentage of gambles (white = 100% gamble). Darker squares indicate a lower percentage of gambles (or a higher percentage of inhibitions; black = 100% inhibition). The bottom graph shows the calculated contrast value for each participant in relation to its mother's State Anxiety score at 12–22 weeks of pregnancy.

Please cite this article in press as: Mennes M et al. Developmental brain alterations in 17 year old boys are related to antenatal maternal anxiety. Clin Neurophysiol (2009), doi:10.1016/j.clinph.2009.04.003

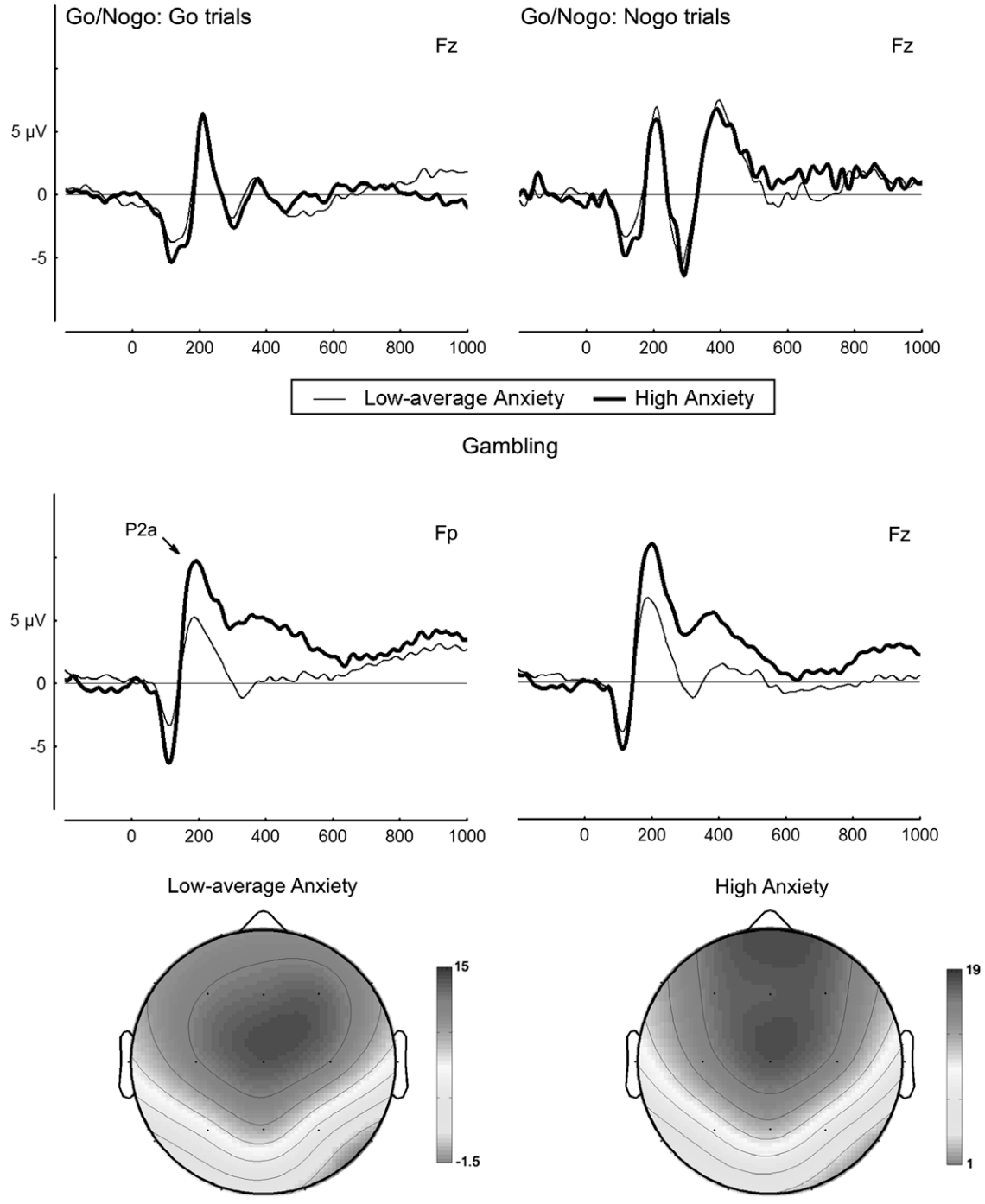

Fig. 2. ERP results for the Go/Nogo and Gambling paradigms. Top: grand-average ERP waveforms at electrode Fz for the Go/Nogo trials. Middle: grand-average ERP waveforms for the Gambling paradigm at electrodes Fp (calculated as the mean of Fp1 and Fp2) and Fz. Averages were made across all trial conditions. Bottom: surface plots showing mean amplitude maps for the N1-to-P2a peak-to-peak values.

3.2.2. Gambling: main effect of anxiety

The adolescents in the high anxiety group showed increased amplitudes at frontal electrodes around 200 ms after stimulus onset (Table 1). At this latency a positive peak was found consistent with the P2a ERP component (Potts, 2004) (Fig. 2). In addition a low-average < high anxiety effect was found around 350 ms after stimulus onset suggesting a difference in the N2 negativity following the P2a. However, ANCOVA on individual P2a-to-N2 peak-to-peak values revealed no significant effect of anxiety. This proves that the SPM significance found at 350 ms was not an independent difference in absolute N2 amplitude but merely reflected the difference found in the preceding P2a.

The P2a results obtained with the SPM analysis were confirmed in an ANCOVA on peak-to-peak values between the P2a peak and the preceding N1 negativity. In accordance with the SPM results, the highest levels of anxiety were associated with the highest P2a amplitudes at the frontal electrodes ($F(11, 198) = 2.77$; $p < .01$). Post-hoc comparisons showed a significantly higher P2a peak for the high anxiety group at electrode Fp2 ($F(1, 18) = 4.88$; $p < .05$), and borderline higher at electrodes Fp1 ($p = .054$), F3

Please cite this article in press as: Mennes M et al. Developmental brain alterations in 17 year old boys are related to antenatal maternal anxiety. Clin Neurophysiol (2009), doi:10.1016/j.clinph.2009.04.003

Table 1
SPM results for the Gambling paradigm. Timing and electrode location of local maxima in clusters of amplitude differences for the low-average < high contrast.

Contrast	Time	Electrode	*t*	*p*	Cluster
Low-average < high	202	Fp1	3.70	<.001	1
	209	Fz	3.61	<.001	
	255	F3	3.54	<.001	
	351	Fp1	4.58	<.001	2
	354	F8	3.51	<.001	3

Notes: Time = time point after stimulus presentation in ms; *t* = *t*-value; *p* = *p*-value.; threshold *t*-value = 3.19. The average smoothness in the data was 49 voxels in the time dimension (i.e. ms) and 3 voxels in the spatial dimension (i.e. electrodes). As such clusters 2 and 3 were interpreted as one effect.

($p = .054$) and F4 ($p = .056$). As for the behavioral results the current effects could not be attributed to outliers (see Supplementary Fig. S1).

3.2.3. Gambling: relationship between anxiety and proportion

Fig. 3 shows that only in the high anxiety group the P2a amplitude increased as the proportional division of the stimulus bar got closer to 50%. This relation was seen at both Fp electrodes and particularly in trials resulting in a gamble (Fig. 3, left panel). Significant Anxiety × Action × Electrode ($F(12, 12432) = 4.87$; $p < .001$) and Anxiety × Proportion × Electrode interactions ($F(60, 12432) = 2.29$; $p < .001$) were found. Post-hoc comparisons yielded a significant linear trend in the high anxiety group for trials resulting in a gamble at electrodes Fp1 ($F(1, 1036) = 49.93$; $p < .001$) and Fp2 ($F(1, 1036) = 42.39$; $p < .001$). This linear trend was weaker in the trials resulting in an inhibition (Fp1: $F(1, 1036) = 3.28$, p = ns; Fp2: $F(1, 1036) = 4.40$; $p = .04$).

4. Discussion

The results presented here suggest that the brain activity of adolescents is related to the level of anxiety experienced by their mother during weeks 12–22 of pregnancy. These effects were present in a gambling paradigm, but not in a Go/Nogo paradigm indicating a specific vulnerability of the development of endogenous cognitive control. The dissociation in the effect of antenatal maternal anxiety on exogenous vs. endogenous cognitive control was evident both in performance and brain activity.

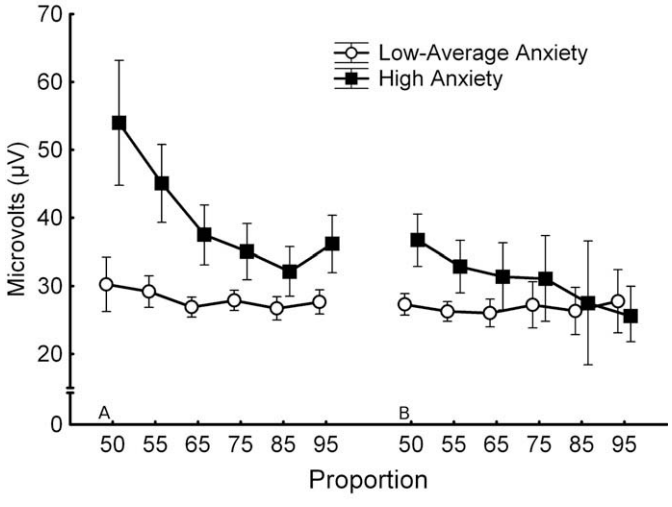

Fig. 3. Relation between the P2a peak at electrode Fp2 and the proportional division of the stimulus bar. (A) Trials resulting in a gamble. (B) Trials resulting in an inhibition. Error bars depict 95% confidence interval of the means.

Antenatal maternal anxiety was not associated with performance on the Go/Nogo paradigm. This confirms our previous finding that exogenous cognitive control is not related to antenatal maternal anxiety (Van den Bergh et al., 2005, 2006; Mennes et al., 2006). Moreover, the absence of an effect of anxiety on the ERPs measured during this task strengthens this conclusion. In contrast, a gambling paradigm typically requires endogenous cognitive control. In order to gain as much points or money as possible, subjects have to decide on the best response based on the relative information provided in each trial, by monitoring their scores, keeping track of previous gains or losses and the length of the task, while inhibiting interfering thoughts. Due to the design of our Gambling task (e.g., reward of 20 points for inhibition) adequate performance is resembled in a characteristic response pattern (Mennes et al., 2008). The pattern observed for the adolescents in the low-average anxiety group matched the response pattern observed in an adult control population (Mennes et al., 2008). The adolescents in the high anxiety group on the other hand, used a different strategy to complete the task. They gambled more in trials where an inhibition is the best option (i.e. trials with a gain $\leqslant$20), but also inhibited more in trials where others rather gambled. As suggested by the trend towards lower total scores this strategy was less optimal.

More importantly, the adolescents in the high anxiety group showed higher amplitudes in the early frontal P2a measured after the gambling stimulus. This ERP component is commonly observed in tasks using visual stimuli, but its functional significance is subject of debate (Luck and Hillyard, 1994; Makeig et al., 1999; Guillem et al., 2001; Potts and Tucker, 2001; Potts, 2004). P2a is generally present in response to targets or task-relevant stimuli and is most consistently interpreted as indexing operations related to the task-relevance of the stimulus (Guillem et al., 2001; Potts and Tucker, 2001; Potts, 2004). Based on these findings it could be argued that the level of antenatal maternal anxiety influences early processing of task relevant information (Kopp et al., 2007). Moreover, the relationship between the P2a amplitude and the probability shown on the stimulus bar, found in the high anxiety group, suggests the color of the stimulus as a possible source for a difference in early processing (Luck and Hillyard, 1994; Taylor and Khan, 2000; Kopp et al., 2007). The adolescents in the high anxiety group might consider color the most relevant feature of the gambling stimulus and therefore focus more on the probability of the bar as indexed by the division between both colored sides instead of examining the complete stimulus.

The effect of anxiety on the P2a is confined to the prefrontal electrodes (Fig. 2), suggesting that our observations might be the product of sources in orbitofrontal cortex (Mennes et al., 2006). However, the exact sources remain speculative due to the low number of electrodes included in the current study and the fact that the scalp distribution does not necessarily reflect the exact location of its underlying sources (Guillem et al., 2001; Potts and Tucker, 2001). Recently, for instance, P2a was linked to sources in medial prefrontal cortex (Potts et al., 2006). Hence, future research with brain monitoring techniques that have a greater spatial resolution compared to ERPs (e.g., fMRI) is needed to confirm our hypothesis.

A slower maturation of the neural sources contributing to the P2a component in the adolescents of the high anxiety group could be underlying the current observations. Developmental studies with visual stimuli in younger children have shown a decrease in P2a amplitude with age until adulthood (Polich, 1997; Taylor and Khan, 2000; Jonkman, 2006). The fact that the prefrontal areas of the brain undergo large developmental changes up into adolescence further supports this hypothesis (Spear, 2000; Paus, 2005). Further research will have to confirm whether the adolescents

Please cite this article in press as: Mennes M et al. Developmental brain alterations in 17 year old boys are related to antenatal maternal anxiety. Clin Neurophysiol (2009), doi:10.1016/j.clinph.2009.04.003

from the high anxiety group can indeed reach full maturation as would be predicted from this hypothesis.

Mainly based on animal literature several mechanisms have been proposed to mediate the association between antenatal maternal anxiety and the development of the fetus and child. A recent study in monkeys suggested that this relationship is mediated through dopamine and dopamine receptors (Schneider et al., 2008). As such antenatal maternal anxiety may influence early neuronal developmental patterns leading to alterations in brain circuitry or synaptic functioning (Coe et al., 2003). This may happen through hormones released by the mother during anxious periods that enter the fetus through the placenta and umbilical cord (Nathanielsz, 1999; Gitau et al., 2001). Finally, there is increasing evidence that environmental influences have an impact on genetically regulated developmental processes (Gluckman et al., 2007). Commonly present, but unexpressed, genes might finally get triggered by higher levels of antenatal maternal anxiety (Rice et al., 2007). Alternatively, genes can be silenced by DNA methylation, induced by prenatal environmental influences (Mill and Petronis, 2008). It is however, a limitation of our study that we did not have genetic information on the adolescents and their mothers.

We also did not include measurements of the adolescents' own anxiety. It is possible that the adolescents in the high anxiety group were more anxious compared to the adolescents included in the low-average group. Anxiety levels or even induced fear have been shown to influence ERP components (Dennis and Chen, 2009; Compton et al., 2007; Moser et al., 2005; Vocat et al., 2008). However, a general or task-induced effect of anxiety might not explain the task specific effects found in the current study. Since we assessed only one run of the Go/Nogo task intermixed with three runs of the Gambling task, anxiety induced by the Gambling task could easily be carried over to the Go/Nogo task. Therefore, if the effects observed in the Gambling task would be an effect of a difference in the adolescents' anxiety, we should at least be able to observe some similar trends in the Go/Nogo results. The almost overlapping ERP waveforms for the low-average and high anxiety group in the Go/Nogo task (Fig. 2) however, show no evidence whatsoever for an effect of anxiety, be it antenatal maternal anxiety or the adolescents' own anxiety.

Another limitation of our study is the relatively small number of subjects in the high anxiety group. Further research with larger sample sizes is needed to confirm our initial findings. Increased sample sizes will also allow including more potential covariates such as smoking during pregnancy, IQ or socio-economic status. Unfortunately, the longitudinal design of our study makes it impossible to include new subjects as we would have no access to data on the level of anxiety experienced by the mothers gathered during pregnancy. Nonetheless, we showed that the differences in gamble performance and P2 amplitude are not due to outliers.

On the other hand, this study has several strengths. First, the inclusion of two paradigms allows us to dissociate between cognitive domains. Second, the use of physiological measures, such as ERP, provides an important impetus for research into the mechanisms of the relationship between antenatal maternal anxiety and subsequent development.

This study has strengthened the hypothesis of a deficit in endogenous cognitive control in adolescents born to mothers who reported high levels of anxiety during weeks 12–22 of pregnancy. These ERP results are the first to relate the level of antenatal maternal anxiety to actual brain functioning in adolescence and underline the importance of environmental influences, even before birth, on neurological development. Further research is needed to gain more insights in the mechanisms underlying the observed association.

Acknowledgements

The authors thank all adolescents and parents for participating, and Heidi Wouters and Jan Vervisch for help with the ERP acquisition. Supported by the Research Foundation Flanders (FWO) (#G.0211.03) and by the K.U.Leuven (IMPH/06/GHW). L.L. is holder of the UCB Chair on Cognitive Dysfunctions in Childhood at the K.U.Leuven.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.clinph.2009.04.003.

References

Bergman K, Sarkar P, O'Connor TG, Modi N, Glover V. Maternal stress during pregnancy predicts cognitive ability and fearfulness in infancy. J Am Acad Child Adolesc Psychiatry 2007;46:1454–63.

Brass M, von Cramon Y. Decomposing components of task preparation with functional magnetic resonance imaging. J Cogn Neurosci 2004;16:609–20.

Brouwers EPM, van Baar AL, Pop VJM. Maternal anxiety during pregnancy and subsequent infant development. Infant Behav Dev 2001;24:95–106.

Coe CL, Kramer M, Czéh B, Gould E, Reeves AJ, Kirschbaum C, et al. Prenatal stress diminishes neurogenesis in the dentate gyrus of juvenile rhesus monkeys. Biol Psychiatry 2003;54:1025–34.

Compton RJ, Carpa J, Chaddocka L, Finemana SL, Quandta LC, Ratliffa JB. Anxiety and error monitoring: increased error sensitivity or altered expectations? Brain Cogn 2007;64:247–56.

Delorme A, Makeig S. EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics. J Neurosci Methods 2004;134:9–21.

Dennis TA, Chen CC. Trait anxiety and conflict monitoring following threat: an ERP study. Psychophysiology 2009;46:122–31.

Durston S, Konrad K. Integrating genetic, psychopharmacological and neuroimaging studies: a converging methods approach to understanding the neurobiology of adhd. Dev Rev 2007;27:374–95.

Gehring WJ, Bryck RL, Jonides J, Albin RL, Badre D. The mind's eye, looking inward? In search of executive control in internal attention shifting. Psychophysiology 2003;40:572–85.

Gitau R, Fisk N, Teixeira J, Cameron A, Glover V. Fetal hypothalamic–pituitary–adrenal stress response to invasive procedures are independent of maternal responses. J Clin Endocrinol Metab 2001;86:104–9.

Gluckman P, Hanson M, Beedle A. Early life events and their consequences for later disease: a life history and evolutionary perspective. Am J Hum Biol 2007;19:1–19.

Guillem F, Bicu M, Debruille JB. Dissociating memory processes involved in direct and indirect tests with ERPs to unfamiliar faces. Cogn Brain Res 2001;11:113–25.

Gutteling BM, de Weerth C, Zandbelt N, Mulder EJ, Visser GH, Buitelaar JK. Does maternal prenatal stress adversely affect the child's learning and memory at age six? J Abnorm Child Psychol 2006;34:789–98.

Jonkman LM. The development of preparation, conflict monitoring and inhibition from early childhood to young adulthood; a Go/Nogo ERP study. Brain Res 2006;1097:181–93.

Jung TP, Makeig S, Humphries C, Lee T, McKeown M, Iragui V, et al. Removing electroencephalographic artifacts by blind source separation. Psychophysiology 2000;37:163–78.

Kopp B, Tabeling S, Moschner C, Wessel K. Temporal dynamics of selective attention and conflict resolution during cross-dimensional go–nogo decisions. BMC Neurosci 2007:8.

Laplante DP, Barr RG, Brunet A, Galbaud du Fort G, Meaney M, Sucier JP, et al. Stress during pregnancy affects general intellectual and language functioning in human toddlers. Pediatr Res 2004;56:400–10.

Liotti M, Pliszka SR, Perez 3rd R, Luus B, Glahn D, Semrud-Clikeman M. Electrophysiological correlates of response inhibition in children and adolescents with ADHD: influence of gender, age, and previous treatment history. Psychophysiology 2007;44:936–48.

Luck SJ, Hillyard SA. Electrophysiological correlates of feature analysis during visual-search. Psychophysiology 1994;31:291–308.

Makeig S, Westerfield M, Jung TP, Covington J, Townsend J, Sejnowski T, et al. Functionally independent components of the late positive event-related potential during visual spatial attention. J Neurosci 1999;19:2665–80.

Mennes M, Stiers P, Lagae L, Van den Bergh B. Long-term cognitive sequelae of antenatal maternal anxiety: involvement of the orbitofrontal cortex. Neurosci Biobehav Rev 2006;30:1078–86.

Mennes M, Wouters H, Lagae L, Van den Bergh B, Stiers P. Detection and resolution of conflict: ERP correlates of complex human decision making. Psychophysiology 2008;45:714–20.

Mill J, Petronis A. Pre- and peri-natal environmental risks for attention-deficit hyperactivity disorder (ADHD): the potential role of epigenetic processes in mediating susceptibility. J Child Psychol Psychiatry 2008;49:11020–30.

Please cite this article in press as: Mennes M et al. Developmental brain alterations in 17 year old boys are related to antenatal maternal anxiety. Clin Neurophysiol (2009), doi:10.1016/j.clinph.2009.04.003

Miller EK, Cohen J. An integrative theory of prefrontal cortex function. Annu Rev Neurosci 2001;24:167–202.
Miller EK. The prefrontal cortex and cognitive control. Nat Rev Neurosci 2000;1:59–65.
Moser JS, Hajcak G, Simons RF. The effects of fear on performance monitoring and attentional allocation. Psychophysiology 2005;42:261–8.
Nathanielsz P. Life in the womb. The origin of health and disease. Ithaca, NY: Promethan Press; 1999.
Nieuwenhuis S, Yeung N, van den Wildenberg W, Ridderinkhof KR. Electrophysiological correlates of anterior cingulate function in a go/no-go task: effects of response conflict and trial type frequency. Cogn Affect Behav Neurosci 2003;3:17–26.
Nigg JT, Knottnerus GM, Martel MM, Nikolas M, Cavanagh K, Karmaus W, et al. Low blood lead levels associated with clinically diagnosed attention-deficit/hyperactivity disorder and mediated by weak cognitive control. Biol Psychiatry 2008;63:325–31.
O'Connor TG, Ben-Shlomo Y, Heron J, Golding J, Adams D, Glover V. Prenatal anxiety predicts individual differences in cortisol in pre-adolescent children. Biol Psychiatry 2005;58:211–7.
Paus T. Mapping brain maturation and cognitive development during adolescence. Trends Cogn Sci 2005;9:60–8.
Polich J. EEG and ERP assessment of normal aging. Electroencephalogr Clin Neurophysiol 1997;104:244–56.
Potts GF, Martin LE, Burton P, Montague PR. When things are better or worse than expected: the medial frontal cortex and the allocation of processing resources. J Cogn Neurosci 2006;18:1112–9.
Potts GF, Tucker DM. Frontal evaluation and posterior representation in target detection. Cogn Brain Res 2001;11:147–56.
Potts GF. An ERP index of task relevance evaluation of visual stimuli. Brain Cogn 2004;56:5–13.
Rice F, Jones I, Thapar A. The impact of gestational stress and prenatal growth on emotional problems in offspring: a review. Acta Psychiatr Scand 2007;115:171–83.
Rubia K, Russell T, Overmeyer S, Brammer MJ, Bullmore ET, Sharma T, et al. Mapping motor inhibition: conjunctive brain activations across different versions of go/no-go and stop tasks. Neuroimage 2001;13:250–61.
Schneider M, Moore CF, Gajewski LL, Larson JA, Roberts AD, Converse AK, et al. Sensory processing disorder in a primate model: evidence from a longitudinal study of prenatal alcohol and prenatal stress effects. Child Dev 2008;79:100–13.
Spear LP. The adolescent brain and age-related behavioral manifestations. Neurosci Biobehav Rev 2000;24:417–63.
Taylor MJ, Khan SC. Top-down modulation of early selective attention processes in children. Int J Psychophysiol 2000;37:135–47.
Van den Bergh B, Van Calster B, Smits T, Van Huffel S, Lagae L. Antenatal maternal anxiety is related to HPA-axis dysregulation and self-reported depressive symptoms in adolescence: a prospective study on the fetal origins of depressed mood. Neuropsychopharmacology 2008;33:536–45.
Van den Bergh BRH, Mennes M, Oosterlaan J, Stevens V, Stiers P, Marcoen A, et al. High antenatal maternal anxiety is related to impulsivity during performance on cognitive tasks in 14- and 15-year-olds. Neurosci Biobehav Rev 2005;29:259–69.
Van den Bergh BRH, Mennes M, Stevens V, Van Der Meere J, Börger N, Stiers P, et al. ADHD deficit as measured in adolescent boys with a continuous performance task is related to antenatal maternal anxiety. Pediatr Res 2006;59:78–82.
Van der Ploeg HM, Defares PB, Spielberger CD. Handleiding bij de Zelf-Beoordelings Vragenlijst ZBV: Een nederlandstalige bewerking van de Spielberger State-Trait Anxiety Inventory, STAI-DY [Manual of the Self-Evaluation Questionnaire: a Dutch version of the State-Trait Anxiety Inventory]. Lisse, The Netherlands: Swets & Zeitlinger B.V.; 1980.
Vocat R, Pourtois G, Vuilleumier P. Unavoidable errors: a spatio-temporal analysis of time-course and neural sources of evoked potentials associated with error processing in a speeded task. Neuropsychologia 2008;46:2545–55.
Wylie GR, Javitt DC, Foxe JJ. Task switching: a high-density electrical mapping study. Neuroimage 2003;20:2322–42.

Please cite this article in press as: Mennes M et al. Developmental brain alterations in 17 year old boys are related to antenatal maternal anxiety. Clin Neurophysiol (2009), doi:10.1016/j.clinph.2009.04.003