Long-term cognitive sequelae of antenatal maternal anxiety: involvement of the orbitofrontal cortex

Maarten Mennes\textsuperscript{a,b}, Peter Stiers\textsuperscript{b}, Lieven Lagae\textsuperscript{c}, Bea Van den Bergh\textsuperscript{a,*}

\textsuperscript{a}Department of Psychology, K.U.Leuven, Tiensestraat 102, 3000 Leuven, Belgium
\textsuperscript{b}Laboratorium voor Neuropsychologie, K.U.Leuven, Medical School, Herestraat 49, 3000 Leuven, Belgium
\textsuperscript{c}Department of Paediatric Neurology, K.U.Leuven, Medical School, University Hospital Gasthuisberg, Herestraat 49, 3000 Leuven, Belgium

Received 23 December 2005; accepted 25 April 2006

Abstract

Anxiety and stress experienced by the mother during pregnancy are reported to have a negative association with the cognitive development of the child. An integration of recent evidence from cognitive reaction time tasks pointed to a deficit in endogenous response inhibition, a function ascribed to prefrontal cortex. To further delineate the cognitive sequelae associated with antenatal maternal anxiety, we reviewed recent neuro-imaging literature to create a cortical map of regions commonly and selectively activated by well-known cognitive tasks. The pragmatic value of this cortical map was tested in a follow-up sample of 49 17-year old adolescents. Adolescents of mothers with high levels of anxiety during week 12–22 of their pregnancy performed significantly lower in tasks which required integration and control of different task parameters. Working memory, inhibition of a prepotent response, and visual orienting of attention were not impaired. Based on the established cortical map, these results were related to subtle developmental aberrations in a part of, or in cortical and sub-cortical regions linked to, the orbitofrontal cortex.

\copyright 2006 Elsevier Ltd. All rights reserved.

Keywords: Pregnancy; Prenatal environment; Functional review; Cognitive deficit; Dual task; Orbitofrontal cortex; Prefrontal map

1. Introduction

An increasing number of studies have reported adverse effects of negative maternal emotions during pregnancy (for example, stress, anxiety or depression) on the...
development of the child (see review Van den Bergh et al., 2005a). Several studies showed an association with fetal behavior (Bartha et al., 2003; DiPietro et al., 2002). Moreover, negative outcomes, such as symptoms of ADHD and other behavioral and emotional disturbances, were shown to persist throughout childhood (O’Connor et al., 2003; Rodriguez and Bohlin, 2005; Van den Bergh and Marcoen, 2004), and even into adolescence (Van den Bergh et al., 2005b, 2006). Furthermore, evidence is building suggesting additional cognitive problems that might underlie some of the behavioral and emotional disturbances. These cognitive problems are manifest by, for example, lower performance on the Bayley Scales of Infant Development, delayed language development and impaired school performance (Brouwers et al., 2001; Huizink et al., 2004; Laplante et al., 2004; Niederhofer and Reiter, 2004).

The present paper was aimed at a better understanding of the nature of the neurocognitive sequelae in children born from mothers who experienced high antenatal anxiety. To this end, we review the available data concerning performance on cognitive tasks in order to delineate more accurately the impairment seen in these children. Since these results point to a prefrontal dysfunction, we will then present an overview of functional magnetic resonance imaging (fMRI) studies with established ‘prefrontal’ (also called executive) cognitive tasks, revealing a map of the functional organization of the lateral prefrontal cortex. Finally, we test the utility of this map and present data obtained with such tasks, administered to 17-year old adolescents of the antenatal maternal anxiety follow-up study of Van den Bergh (Van den Bergh and Marcoen, 2004; Van den Bergh et al., 2005b, 2006). Based on the functional map of the prefrontal cortex, these data will allow us to further delineate the cognitive impairments seen in the high antenatal maternal anxiety group, both in terms of the cognitive processes involved and the prefrontal areas most likely affected by antenatal maternal anxiety.

2. Cognitive repercussions of antenatal maternal anxiety: endogenous response control

Only recently a first attempt was made to study long-term cognitive consequences of antenatal maternal anxiety using reaction time tasks. At the age of 14–15 years children of mothers who experienced high levels of anxiety during weeks 12–22 of their pregnancy were found to respond more impulsively in a task assessing divided attention (Van den Bergh et al., 2005b). Regardless of the task conditions, in a matching-to-sample task with four simultaneously presented letters, these adolescents responded significantly faster compared to a control group of adolescents from mothers experiencing low to moderate levels of anxiety during pregnancy. In addition, they made more errors, particularly in trials with no targets (‘false alarms’), in which all four letters had to be processed before an adequate response could be given. This pattern of reacting faster, but with more errors is indicative of impulsive responding. In contrast to this interpretation, the same adolescents did not differ from the control group on a ‘Stop’ task, which is typically used to assess response inhibition. They were equally able as the control group to inhibit a prepotent response contingent upon an external stimulus. To reconcile these seemingly opposite results, the authors hypothesized that the impulsivity seen in adolescents of the high antenatal maternal anxiety group is confined to conditions requiring endogenous as opposed to exogenous response control. In the Stop task, an external signal triggers the inhibition of the prepared key-press. The non-target trials of the matching-to-sample task, on the other hand, required the subject to withhold the hit-response long enough to be able to process all four letters. This continued inhibition has to be generated endogenously, from within the subject. Support for this interpretation was provided by a second study with the same group of adolescents (Van den Bergh et al., 2006). Endogenous response control was assessed using a continuous performance task consisting of a simple Go/NoGo target-search task (detecting Qs among Os) but with only 57 targets in a test lasting 24 min. A slow presentation rate and variable inter-stimulus interval, to exclude anticipation of the next trial, further increased the amount of endogenous inhibition required. This task is typically used to assess an underlying cognitive regulation disorder in children with attention deficit/hyperactivity disorder (Berwid et al., 2005; Van der Meere et al., 1995). Adolescent boys of mothers who experienced high antenatal anxiety showed greater response variability compared to the control group towards the end of the long and tedious session. As the task required the ability internally to inhibit reactions to interfering and distracting internal or external stimuli in the absence of a motivating and performance-stimulating paradigm, it was concluded that the boys of the high antenatal maternal anxiety group showed an impairment in endogenous response control. In addition, Van den Bergh et al. (2005b) manipulated the working memory load in the matching-to-sample task. However, they found that a greater load on working memory did not differentially affect performance of the adolescents in the high compared to the low-average antenatal maternal anxiety group.

Although it is generally accepted that higher cognitive processes such as endogenous response control are associated with the prefrontal cortex (Miller, 2000; Koehl et al., 2003), the particular subdivisions of prefrontal cortex that may be more critical are less clear, and may depend on the nature of the particular processes under endogenous control. It has, for instance, been shown that the supplementary motor areas and anterior cingulate cortex are involved in the endogenous generation of rhythmic motor patterns, whereas when the same motor patterns are exogenously paced by external stimuli there is greater activation in the premotor area (Jenkins et al., 2000; Thut et al., 2000). Voluntary and thus endogenous shifts of visual attention on the other hand, activated more
dorsolateral and ventrolateral prefrontal areas compared to externally triggered shifts of attention, which activated occipital regions (Coull et al., 2000). Finally, patients with obsessive–compulsive disorder, which have been shown to have orbitofrontal abnormalities (McGuire et al., 1994; Saxena et al., 1999), responded more impulsively on a continuous performance task, and showed reduced frontal activity during the inhibition trials (Herrmann et al., 2003).

Considering these studies and the first evidence for specific cognitive impairments related to high antenatal maternal anxiety, it is plausible that high antenatal maternal anxiety may interfere with normal development and functioning of the prefrontal cortex.

3. Organization of cognition in the lateral prefrontal cortex

Since the data discussed above seem to point to a selective dysfunction associated with the prefrontal cortex, our goal was to examine whether this dysfunction could be linked more accurately to designated subregions of the prefrontal cortex. Several general theoretical models have been proposed for the functional organization of the prefrontal cortex (Faw, 2003; Fuster, 2001; Koechlin et al., 2003; Miller and Cohen, 2001). These models divide this vast region of cerebral cortex in larger subregions and attempt to characterize the nature of processes and their interactions taking place in each of the subregions. Such global theoretical models are not always useful in coming to understand the relationship between dysfunction and brain structure in the case of particular patient populations. Therefore, we used a pragmatic approach to the characterization of the functional organization of the prefrontal cortex, by reviewing the relationship between established prefrontal cognitive tasks and the areas in the prefrontal cortex selectively involved while performing these tasks. Fig. 1 integrates the results of 16 recent representative fMRI studies covering 5 typical prefrontal cognitive tasks (i.e., N-back matching, Go/NoGo, cued attention, dual task, and response-shifting) (Cohen et al., 1997; Corbetta et al., 2002; Dreher and Grafman, 2003; Garavan et al., 2002, 2003; Horn et al., 2003; Kelly et al., 2004; Kincade et al., 2005; Koechlin et al., 1999; Kondo et al., 2004; Menon et al., 2001; Peelen et al., 2004; Thiel et al., 2004; Sylvester et al., 2003; Szameit et al., 2002; Veltman et al., 2003). Inclusion was limited to those studies that presented original fMRI data, that reported Talairach and Tournoux co-ordinates (Talairach and Tournoux, 1980) has been administered to the infants born from mothers experiencing high levels of anxiety during their pregnancy studied previously by Van den Bergh et al. (Van den Bergh and Marcoen, 2004; Van den Bergh et al., 2005b, 2006).

4. Delineating cognitive sequelae of high antenatal maternal anxiety

Of the 64 adolescents who participated in the cognitive assessment at age 14/15 (Van den Bergh et al., 2005b, 2006), 49 participated in the new study. These included 13 of the 16 subjects of the high anxiety group of the former study. All subjects were 17 years old (M = 17 years 6 months, SD = 3 months). The sample comprised 29 boys and 20 girls. All participants were born in the same hospital between 36 and 41 weeks of gestation with a mean birth weight of 3236 g (SD = 560) and 5 min Apgar scores of 9 or 10. The local ethical committee for experiments on human subjects approved the study. All participants gave their written informed consent.

The procedures used to assess antenatal maternal anxiety have been described in detail elsewhere (Van den Bergh and Marcoen, 2004; Van den Bergh et al., 2005b). In short, the Dutch version of the State Trait Anxiety Inventory (STAI; Van der Ploeg et al., 1980) has been administered to the randomly selected sample of mothers at 12–22, 23–31 and 32–40 weeks of pregnancy. Because the state anxiety subscale provides a valid measure of the intensity of transitory anxiety in response to real life stress, this subscale was used to investigate the effects of antenatal maternal anxiety. The cut-off used to delineate the high from the low-average anxiety group was a state anxiety score at week 12–22 above or equal to 43. This is the same value as used in the study at age 14/15. As in the previous
study, this cut-off value represented the 25% highest anxiety scores of the present sample. This resulted in 15 participants in the high anxiety group (10 boys, 5 girls) and 34 in the low-average anxiety group (19 boys, 15 girls).

Table 1 summarizes the different neurocognitive tasks used to delineate the cognitive consequences of antenatal maternal anxiety. They were based on the tasks used in the fMRI studies included in the review of the cortical organization of prefrontal cognitive functions presented in Section 3. The tasks used were a Cued Attention, N-back, Go/NoGo Task, Dual Tasks, and a Response-Shifting Task. To control for possible differences in general non-verbal cognitive abilities between both groups the nonverbal subscale of the WAIS-III intelligence scale was administered. The verbal subscale was not included because verbal cognitive abilities are less relevant for the cognitive tasks used in the present study, which are non-verbal performance tasks in nature.

Data were analyzed using analysis of covariance (ANCOVA). Maternal State Anxiety at 12–22 weeks (Anx12–22), 23–32 weeks (Anx23–32) or 33–40 weeks (Anx33–40) of pregnancy were used as independent variables in addition to gender, in three separate analyses of the data. Depending on the task within-subject factors were included. To control for a possible influence of anxiety during other periods of pregnancy than the one included as independent variable, the state anxiety measures in the other two periods and a component incorporating postnatal maternal anxiety measured at each stage of our longitudinal study were included as covariates. In addition, the non-verbal IQ-score of the adolescents as measured with the WAIS-III was included as a covariate. All dependent variables were log-transformed to improve normal distribution. A significance level of 0.05 was used.

It was found that only antenatal maternal anxiety during weeks 12–22 of pregnancy was related to measures of cognitive control and internal response control. Adolescents of mothers who experienced high anxiety during weeks 23–32, and weeks 33–40 did not differ from adolescents of mothers with low to average levels of antenatal anxiety in the same period on any of the cognitive measures.

Working memory (N-back task) and external inhibition of a prepotent response (Go/NoGo task) were not related to antenatal maternal anxiety ($F[1,41] < 0.13$ and $F[1,41] < 0.35$, respectively). This strengthens the conclusions drawn by Van den Bergh et al. (2005b, 2006), since the tasks used here are standard measures of these prefrontal cognitive functions. Moreover, the cued visual attention task, which was not used before in this research...
population, also revealed no relationship with antenatal maternal anxiety, indicating that adolescents of mothers with high levels of anxiety during pregnancy have no difficulties with visual orienting and reorienting of attention ($F[1,41] = 1.5$). Thus, these adolescents did not show any dysfunction on three different cognitive tasks that are critically dependent upon several subregions of the prefrontal cortex.

In contrast, adolescents of mothers with high antenatal anxiety during weeks 12–22 of their pregnancy scored significantly lower compared to adolescents of mothers with normal levels of antenatal anxiety on measures of cognitive control. First, the percentage of correct answers in the Shifting Attentional Set—Visual task was overall lower in the high antenatal maternal anxiety group ($F[1,41] = 5.34$, $p = 0.026$). However, there was a significant three-way interaction between anxiety, compatibility and shifting ($F[1,41] = 5.78$, $p = 0.021$). As can be seen in Fig. 2, when no shifting was required, the adolescents of the high anxiety group performed worse on the incompatible (but not on the compatible) response blocks compared to the control group. When shifting was required, they made more errors compared to the control group both on the compatible and the incompatible trials. This confirms the conclusion of Van den Bergh et al. that high antenatal maternal anxiety is associated with reduced endogenous response inhibition. In the second part of this task, the subjects had to make a response opposite to that learned in part 1. Since this inversion had to be maintained throughout the second part, the subjects had to signal to themselves endogenously to inhibit the response learned in part 1 upon each move of the square. This simple endogenous response control requirement already increased their error rate compared to the low-average anxiety group.

The second specific cognitive deficit was that the adolescents in the high maternal anxiety group showed a decrease in performance when the cognitive load of the task was increased in the Dual Tasks (Fig. 3). Adolescents from mothers with a low-to-average level of antenatal anxiety worked as efficient when they had to combine visual search and sound counting in the Sky Search Dual task, as when they had to do the search task alone. Adolescents in the high antenatal maternal anxiety group, on the other hand, slowed down significantly when the sound-counting task was added ($F[2,82] = 3.38$, $p = 0.039$). A similar trend, albeit not significant, could also be seen in the auditory dual task Elevator Counting with Distraction ($F[1,41] = 0.25$). These results suggest that the adolescents in the high antenatal anxiety group experienced difficulties organizing their cognitive resources in order to handle two tasks at the same time. This may also explain why the adolescents in the high antenatal anxiety group made significantly more errors in all, but the easiest condition of

<table>
<thead>
<tr>
<th>Task</th>
<th>Description</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cued attention</td>
<td>Visual cued-attention orientation task. 20% invalid cues (Corbetta et al., 2002; Posner, 1980)</td>
<td>Reaction time Percentage correct</td>
</tr>
<tr>
<td>N-back</td>
<td>Assesses working memory. Is the presented stimulus the same as the stimulus presented one (1-back) or two (2-back) presentations prior to the current stimulus? 0-back (press key if a particular stimulus appears) to assess baseline performance</td>
<td>Reaction time Percentage correct</td>
</tr>
<tr>
<td>Go/NoGo</td>
<td>Assesses the ability to inhibit a prepotent response contingent upon an external cue. 80% Go-trials.</td>
<td>Reaction time Percentage correct</td>
</tr>
<tr>
<td>Response-shifting</td>
<td>Shifting Attentional Set—Visual (de Sonneville, 1999). Part 1: press key in correspondence to movement of a green-colored square (Compatible Condition); Part 2: press key opposite to movement of a red-colored square (Incompatible Condition); Part 3: combination of part 1 and 2, random alternation between green and red squares (Shifting Condition, with Compatible and Incompatible trials)</td>
<td>Reaction time Percentage correct</td>
</tr>
</tbody>
</table>
the response-shifting task (Fig. 2). Whenever the cognitive demand of the task was increased by adding a complicating task requirement to the basic paradigm, their performance deteriorated.

5. Mapping the affected prefrontal cortical region(s)

The cognitive capacities needed to optimally perform in the dual task and response-shifting task could be generally labeled as cognitive control (Miller, 2000; Koechlin et al., 2003). Subjects are required to perform two tasks simultaneously, integrate or switch between different task rules or integrate current information with information held on line in working memory. This ability cognitively to control, coordinate and integrate different task variables is commonly attributed to the prefrontal cortex. As presented in Fig. 1, we found a consistent mapping of cognitive functions based on a review of recent fMRI literature (Cohen et al., 1997; Corbetta et al., 2002; Dreher and Grafman, 2003; Garavan et al., 2002, 2003; Horn et al., 2003).
2003; Kelly et al., 2004; Kincade et al., 2005; Koechlin et al., 1999; Kondo et al., 2004; Menon et al., 2001; Peelen et al., 2004; Thiel et al., 2004; Sylvester et al., 2003; Szameitat et al., 2002; Veltman et al., 2003). According to this functional map, the cognitive profile observed in the adolescents of the high Anx12–22 group would be compatible with a dysfunction in the dorsal part of the orbitofrontal cortex and more specifically in BA 10 and the lower part of BA 46 (the region indicated in blue in Fig. 1). Although several other areas were activated by dual- and response-shifting tasks, this part of the orbitofrontal cortex was found to respond only during performance on these two tasks, and not during performance on the other cognitive tasks used.

Damage to the orbitofrontal cortex is usually associated with emotional-behavioral disturbances. Such patients show impulsive and inappropriate behavior, have problems processing the hedonic value of stimuli and have difficulties reversing reward–behavior associations (Berlin et al., 2004; Hornak et al., 2004; Kringelbach, 2005). Only very few studies have investigated the contribution of this part of the prefrontal cortex to cognitive performance. In two studies working memory was assessed and neither reported an impairment in patients with damage to orbitofrontal cortex, whereas they did find working memory deficits in patients with dorsolateral and dorsomedial prefrontal lesions (Berlin et al., 2004; Manes et al., 2002). This is in agreement with the present findings.

Although the present review of the literature and the supporting new data both point to a designated part of the prefrontal cortex as the possible neural correlate for the dysfunctions seen in adolescents with high antenatal maternal anxiety, this does not preclude the involvement of other parts of the prefrontal cortex. Particularly, regions on the ventral and medial side of the prefrontal cortex have been shown to be involved in such abilities as time perception, planning, learning and reversing stimulus-reinforcement associations, etc. (Berlin et al., 2004; Fuster, 2001; Hornak et al., 2004; Miller and Cohen, 2001). Since in the present study we did not include tasks to evaluate these functions, no conclusions can be drawn in this respect.

Finally, it should be noted that the delineation of a cortical region involved in the observed cognitive deficit is only indirect and the apparent link described here may be secondary to intermediate processing deficits elsewhere in the cerebral and subcortical networks. Functional MRI and evoked potential studies are required to provide direct evidence of a functional abnormality in the delineated region and/or possibly other brain regions.

6. The timing of anxiety and possible mechanisms

Anx12–22 was the only pregnancy period during which high maternal state anxiety yielded a significant effect. This corroborates the previous findings of this follow-up study (Van den Bergh and Marcoen, 2004; Van den Bergh et al., 2005b, 2006). For our study sample the period between 12 and 22 weeks of pregnancy or at least before the 22nd week of gestation clearly is the most critical in generating unfavorable cognitive outcome, discernible even up to 17 years later. The finding of a specific time window makes it unlikely that the associations found can be explained by genetic mediations only, as this does not explain why effects only involved anxiety at 12–22 weeks of pregnancy and not prenatal anxiety at 23–31 or 32–40 weeks or postnatal anxiety. It is plausible that physiological events involved in high antenatal maternal anxiety triggered gene regulatory mechanisms and the expression of specific genes, transferred from mother to fetus. If this were the case, it would underline the importance of anxiety as prenatal environmental factor (Gottlieb and Halpern, 2002; Grossman et al., 2003; Rutter et al., 1999).

Several studies also reported associations with early pregnancy periods (Huizink et al., 2004; Laplante et al., 2004; Martin et al., 1999; Rodriguez and Bohlin, 2005). Other studies on the other hand found associations with later periods during pregnancy (Brouwers et al., 2001; O‘Connor et al., 2002, 2003). However, negative effects were not always confined to a specific period during pregnancy, or even consistent with respect to the critical period, and not all studies included a range of pregnancy periods (Brouwers et al., 2001).

It is generally thought that when mechanisms mediating the effects of antenatal anxiety or stress operate during critical time windows of development, they alter the ongoing brain developmental processes (Gluckman and Hanson, 2004; Wadhwa, 2005). Although in humans it is currently not possible to investigate directly, it is plausible that anxiety-related hormones interfere with the neuro-developmental processes—neuron proliferation, migration and differentiation—taking place in between, or before, week 12 and 22 of pregnancy. This could lead to subtle aberrations of normal development possibly inducing the observed effects on cognitive control, especially since during this period several important brain-structures (hippocampus, amygdala, anterior cingulate cortex) connected to the prefrontal cortex differentiate (Garel, 2004; Nowakowski and Hayes, 2002). Such effects have been documented in animal research. (Koo et al, 2003; Van den Hove et al., 2006)

7. Conclusion

It is well established that a mother’s negative emotions during pregnancy have adverse effects on the cognitive, behavioral and emotional development of the child. In the present study we tried to delineate more accurately the nature of the cognitive consequences of high antenatal maternal anxiety, making use of a functional map of prefrontal cortex and the well-established prefrontal tasks from which it was derived. It was found that adolescents of mothers experiencing high levels of anxiety during pregnancy performed selectively lower in tasks with a greater
load on cognitive control, which was found to be linked to orbitofrontal cortex. Further studies using both imaging and cognitive assessment are needed to investigate whether the source for these observations is truly located within orbitofrontal cortex and its networks.

Acknowledgments

We wish to thank all adolescents and their parents for participating, and Heidi Wouters and Michelle Vanden Boer for their assistance and valuable comments. This research is supported by Grant no. G.0211.3 of the Fund for Scientific Research Flanders (FWO). L. Lagae is holder of the ‘UCB Chair on Cognitive Dysfunctions in Childhood’ at the Catholic University of Leuven.

References


