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Review

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

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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.

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

Contents

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

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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; Koechlin 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