Neurobiological and behavioral stress reactivity in children prenatally exposed to tobacco

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Summary This study examined neurobiological and behavioral stress reactivity in children who had been prenatally exposed to tobacco. Neurobiological stress reactivity was measured using salivary cortisol and alpha-amylase levels at five different time points throughout a stressful neuropsychological test session, which involved a competition against a videotaped opponent. Participants (mean age: 10.6 years, SD 1.3) were 14 prenatally exposed (PE) children, 9 children with disruptive behavior problems (DBD), and 15 normal controls (NC). For cortisol responses, no significant differences between the three groups were observed. Normal controls, however, had significantly higher alpha-amylase levels than PE-children throughout the test session, and their alpha-amylase levels also increased throughout the session, whereas these remained low and stable for PE-children. Alpha-amylase levels and trajectory of PE-children were similar to those observed for DBD-children. PE-children also showed significantly increased behavioral stress reactivity compared to NC-children, and neurobiological and behavioral stress reactivity were inversely related in PE-children, again similar to what was observed for DBD-children. These results support the hypothesis that prenatal smoking may lead to long-lasting neurobiological and behavioral changes in exposed offspring.

1. Introduction

Prenatal tobacco exposure has been related, in both and animal and human studies, to structural and neurobiological changes in the offspring brain. These changes include cortical thinning (e.g., of the orbitofrontal cortex) (Toro et al., 2008), smaller volume of specific brain structures (e.g., the corpus callosum (Paus et al., 2008), disruptions of white matter
Acetylcholine and norepinephrine are neurotransmitters with specific functions in the nervous system. Nicotine exposure experienced prenatally has stopped a mechanism that under-stimulated after conception because the direct cholinergic and catecholaminergic activity, as the nAChRs will also lead to systematic or functional down-regulation (of both increases in numbers of receptors, specifically nAChRs, will have further (indirect) effects on neurotransmitter availability (Oncken et al., 2003). Both structural damage and in- and decreases in receptor density are likely to have functional consequences. Whereas structural damage and reductions in receptor density may be relatively easy to associate with systematic or functional down-regulation, an important hypothesis in the context of prenatal tobacco exposure is that receptor density may be relatively easy to associate with systematic or functional down-regulation (of both cholinergic and catecholaminergic activity), as the nAChRs will be under-stimulated after conception because the direct nicotine exposure experienced prenatally has stopped (Oncken et al., 2003). Acetylcholine and norepinephrine are the two most important neurotransmitters for functioning of the hypothalamic—pituitary—adrenal (HPA-) axis and the Sympathetic Nervous System (SNS), which are both involved in stress regulation. The SNS is part of the autonomic nervous system and is involved in quick (fight-or-flight type) reactions to stress; at the hormonal level its activity is represented by the enzyme alpha-amylase, for which increases can be observed immediately after a stressor. Compared to the SNS, the HPA-axis has more reciprocal connections with cortical structures involved in cognitive-emotional control and memory, such as the orbitofrontal cortex and the hippocampus: in humans, its activity is generally represented by (changes in) the hormone cortisol, which reaches its peak level approximately 20–30 min after a stressor.

Based on the evidence for PE-related changes to brain structures and neurotransmitter systems important for stress regulation, it may be hypothesized that children of mothers who smoked during pregnancy will have altered stress reactivity. Studies to date have indeed provided indications that this is the case. Behaviorally, it was shown that PE-children had less frustration or stress tolerance than non-exposed controls during delays in a (simple) cognitive task (Huijbregts et al., 2008a). Findings regarding neurobiological stress reactivity are mixed, with reports of increased cortisol reactions in PE-children (Schuetze et al., 2008) and reports of the absence of any difference in cortisol and alpha-amylase activity with non-exposed children (Granger et al., 2007). There are also reports showing reduced physiological stress reactivity in exposed children, although these generally used non-hormonal measurements, such as different heart rate indices (Fifer et al., 2009). An important consideration here might be that these studies almost exclusively focused on infants, whose stress systems work differently from those of older children and whose (neurobiological) stress reactivity may also change following (continuously) high exposure to stress hormones early in life (from hyper-reactive to hypo-reactive: Miller et al., 2007). This is the first study to investigate hormonal stress reactivity (in combination with mood changes and behavioral stress reactivity) in exposed children from an older age group. For this group we hypothesize lower neurobiological stress reactivity compared to controls, in part based on the evidence suggesting reduced functional activity of cholinergic and catecholaminergic systems. We further expect to replicate our earlier finding of behavioral hyper-reactivity in the exposed group (Huijbregts et al., 2008a), more negative moods and more extreme mood changes.

A similar discrepancy between neurobiological and behavioral stress reactivity has been reported for children with disruptive behavior disorders (DBDs) (Van Goozen et al., 2000, 2007; Ortiz and Raine, 2004) Prenatal tobacco exposure has repeatedly been related to externalizing behavior problems in children, even when controlling for other established risk factors, but the mechanisms underlying this association are still unclear (Wakschlag et al., 2006; Huijbregts et al., 2008b). Altered patterns of behavioral and neurobiological stress reactivity in exposed children might, in part, explain their elevated levels of externalizing behavior. Thus, our two main research questions were (1) do children prenatally exposed to tobacco have altered stress reactivity, both neurobiologically and behaviorally? and (2) does stress reactivity of children prenatally exposed to tobacco resemble that of children with DBDs?

2. Methods

2.1. Participants

One-hundred-and-fifty children aged 8—13 from three regular primary schools and their families received an invitation to take part in the study. Out of 90 potential participants (i.e., those who expressed their willingness to participate), all children were selected whose mother indicated she had smoked during pregnancy (PE: N = 14, mean age: 10.6, SD 1.6) and all children whose mother indicated relatively high levels of disruptive behavior (i.e., a score of 12 or higher on "aggressive behavior" plus "rule-breaking behavior" for all girls and for boys aged 11 or younger, or a score of 14 or higher for boys aged 12 or older) on the child behavior checklist (CBCL, Achenbach, 1991) (DBD: N = 9, mean age: 10.5, SD 1.3). Normal controls (N = 15, mean age: 10.6, SD: 1.2) were matched to the PE- and DBD-children on age and gender. Thus, in total thirty-eight children (22 boys (PE: 7; DBD: 7; NC: 8); 16 girls (PE: 7; DBD: 2; NC: 7) took part in this study. Written informed consent was obtained from the parents of all children. Ethical approval for this study was granted by Leiden University’s Education and Child Studies Ethics Committee.

2.2. Procedure

Participants performed 9 neuropsychological computer tests (De Sonneville, 1999) during a session lasting approximately 90 min. During the test session, a situation of competition was created between the subject and a videotaped opponent (i.e., an actor not really involved in the competition). The video-opponent criticized the performance of the participant in a competitive and derogatory way. The rationale behind choosing this stress paradigm (based on Van Goozen et al., 2000) was that it has been shown that neurobiological stress responses are most pronounced when tasks are characterized by 'uncontrollability' and social-evaluative threat (i.e., task performance can be judged negatively by others) (Dickerson and Kemeny, 2004). Uncontrollability was introduced in two of the tasks: the Delay Frustration task, a relatively simple work-
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